The neuropsychological and behavioural profiles of HIV-infected asymptomatic HAART-naïve children: A cross sectional and follow-up study

Victoria Webster
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Supervisor: Leigh Schrieff
Co-supervisor: Kevin G. F. Thomas, PhD.
Faculty of Humanities
University of Cape Town
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Compulsory declaration

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and in quotation in, this dissertation for the work, or works, of other people has been attributed, and has been cited and referenced.

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ABSTRACT

Background. One of the most serious consequences of pediatric HIV infection is its impact on the central nervous system (CNS). Children born with HIV may present with cognitive abnormalities within a few months or years of birth. However, there are a group of children known as 'slow progressors' or asymptomatic children who do not exhibit typical symptoms of HIV and are consequently not put onto Highly Active Antiretroviral Therapy (HAART). Research focusing on this subset of asymptomatic HAART-naïve children is limited. *Aims.* The current study is divided into two studies. Study 1 sought to explore the cognitive and behavioural profiles of asymptomatic HAART-naïve children in comparison to a matched HIV-negative control group. Study 2 was a follow up study, 10-12 months later, of a subset of the children in study 1. *Methods.* The sample in study 1 consisted of 12 HIV-infected asymptomatic HAART-naïve children, ages 6-12, from low SES backgrounds and who were Xhosa speaking (one English speaking participant). A comprehensive battery of neuropsychological tests was used to test general intellectual functioning as well as specific cognitive domains. The Child Behaviour Checklist was used to assess behaviour. In study 2, the sample consisted of five children from the original study and the same measures were used. *Results.* Study 1 showed that the HAART-naïve group performed similarly to the control group in terms of general intellectual functioning and some cognitive impairment were noted in specific cognitive domains of executive function, motor function and attention. Some behavioural difficulties were noted, such as internalizing and school related difficulties. In study 2, there was no clear pattern of consistent improvement or decline for either cognitive or behavioural functioning. *Conclusions.* Asymptomatic HAART-naïve children may not exhibit typical symptoms of HIV, but is suggested that they do experience some underlying CNS impairments and behavioural difficulties. This research serves to demonstrate that these difficulties need to be taken into account so that the appropriate services can be made available for the proper care and management of asymptomatic HAART-naïve children.

Keywords: asymptomatic, pediatric HIV, HAART, children, CNS.

LITERATURE REVIEW

The Human Immunodeficiency Virus (HIV) has a severe impact on the lives of children throughout the world. At the end of 2009, it was estimated that, worldwide, 2.5 million children were living with HIV and that there were approximately 420,000 new infections each year among infants and children (Kovacs, 2009). One of the most serious consequences of HIV infection is its impact on the central nervous system (CNS). This results in neurocognitive abnormalities, both in adults and children (Kovacs, 2009). Children born with HIV (perinatal or vertical transmission) may begin to present these abnormalities within a few months of birth. However, there are other children born with HIV who may only present with HIV-related symptoms and cognitive deficits in late childhood and early adolescence. These children are referred to as asymptomatic HIV-infected children (Dunkley-Thompson, Figueroa, & Christie, 2006). Research focusing on purely asymptomatic children has rarely been reported in literature and it is suggested that these children make up a small subset of the HIV-infected paediatric population (Judd et al., 2009).

Antiretroviral drugs, more specifically Highly Active Antiretroviral Therapy (HAART), may inhibit the progression of HIV, improving general health and daily functioning (Brown & Lourie, 2000). HIV-infected children who may only present with cognitive deficits later in life are not treated with HAART while they remain asymptomatic and are therefore referred to as being HAART-naïve. In resource-limited countries, such as South Africa, the number of children with access to HAART is unknown, although it is estimated to be very low (Meyers et al., 2007). Therefore, South Africa provides a population of HAART-naïve children, some of whom will be asymptomatic, without any previous exposure to antiretroviral drugs. Despite this potentially large population of asymptomatic HAART-naïve children in South Africa, children can rapidly progress to symptomatic HIV infection and will consequently (if HAART is available to them) be put onto HAART. Additionally, if families can afford private medical care, HAART can, in some cases, be initiated in asymptomatic children.

Both cross-sectional and longitudinal studies of the behavioural and cognitive profiles of asymptomatic HAART-naïve children are limited and further research is needed in this field. This kind of research will provide a more comprehensive picture of how disease presentation and progression manifests in asymptomatic HAART-naïve children, thereby contributing to the literature on HIV-infected children in general.

HIV infection and CNS-related consequences

HIV, the virus that develops into Acquired Immune Deficiency Syndrome (AIDS), was initially thought to only affect the immune system (Byers, 2001). We now know, however, that HIV-infection has a direct impact on the CNS, causing the development of CNS-related disease and disorders. This impact can manifest in a variety of ways, ranging from mild cognitive impairment of general intellectual functioning to severe deficits in specific cognitive domains. It may also manifest in behavioural and emotional impairment (Kovacs, 2009).

Neuropsychological manifestations of HIV-infected children

Many studies have focused on the neuropsychological consequences of HIV infection in the adult brain; however this research cannot simply be applied to HIV-infected children. The neuropsychological impact of HIV on the adult brain differs to the impact seen in children, with regard to developmental deficits, progression and severity of disease. HIV infection acquired by vertical transmission occurs when the immune system is at its most immature and still undergoing development. HIV-infected symptomatic children with this type of transmission have earlier and more severe manifestations of CNS disease and a more rapid disease progression than adults (Kovacs, 2009). Although HIV infection may impact the developing brains of different children in unique ways, there are general neurological manifestations of HIV in the developing brain of typically symptomatic children. These include impaired brain growth, loss or plateauing of developmental milestones and progressive motor dysfunction. Typically, associated impairments are found in other cognitive domains, such as the domains of language and attention. Global neurocognitive impairments have not been typically identified in HIV-infected symptomatic children and behavioural and social-emotional deficits have also been reported (Willen, 2006). In summary, developmental abnormalities manifested by neurological and neuropsychological problems are characteristic of children with symptomatic HIV infection (Wolters, Brouwers, Civitello & Moss, 1997).

It is commonly believed that CNS abnormalities associated with vertically infected children are primarily caused by direct infection of macrophages and microglia by the HIV virus. It is hypothesized that this infection leads to neurotoxicity, neuronal damage and disturbances between cells, thus causing structural abnormalities (Willen, 2006). The most common structural abnormalities include cortical atrophy, basal ganglia calcifications and white matter (including frontal white matter) irregularity (Van Rie, Harrington, Dow &

Robertson, 2007). These structural abnormalities, which are common consequences of HIV infection, have been shown to be the direct impact of the HIV infection on the brain (Wachsler-Felder & Golden, 2002) and are often captured through neuroimaging techniques. CT and MRI scans have proven helpful in documenting the effects of HIV on the CNS. These structural abnormalities are compatible with the clinical manifestation seen in children with HIV. These clinical manifestations range from impaired memory, concentration and processing speed, to the more advanced stages of brain deterioration where general intellectual functioning is impaired as well as verbal and motor responses. These changes can be attributed to the significant loss of neurons in the frontal cortex as well as to subcortical damage. It is therefore fitting that neuropsychological investigations have suggested that measures of frontal subcortical functioning may be particularly sensitive measures of HIV-related cognitive decline (Lopez-Villegas, Lenkinski & Frank, 1997). Furthermore, damage to the basal ganglia is commonly associated with motor impairments and higher order cognitive functioning (Berger & Arendt, 2000). The clinical manifestations mentioned above will be discussed in further detail as they apply to asymptomatic HAART-naïve children specifically.

Treatment of HIV infection

As mentioned above, HIV-infected children can develop severe cognitive deficits that impact upon their daily functioning. The introduction of HAART, defined as a combination of at least three antiretroviral drugs, is recommended for the treatment of HIV-related symptoms, such as a lowered immune system, nausea, headaches and body aches (Koekkoek et al., 2006). It has been suggested that HAART improves the immune system, increasing the CD4 count (white blood cells) in children. 30 Studies done in Sub-Saharan Africa describe the treatment outcomes of previously untreated children who were put onto HAART. Treatment outcomes suggested that their nutritional status improved over time, with the majority of studies finding significant improvement in immunological status of these children (Sutcliffe, van Dijk, Bolton, Persaud & Moss, 2008). Furthermore, studies describing HIV-infected African children's immunological response to HAART have shown that over a two-year period these children's immune systems improved and there was a decrease in viral load. In general a low mortality rate was achieved (Rouet et al., 2006).

While it seems that HAART may improve immunological status, the effects that HAART has on the CNS are not entirely known. There has been some suggestion that HAART may be positively related to cognitive functioning, and may aid in improving

neuropsychological functioning or at least prevent more severe forms of HIV-associated neurocognitive disorders (Singh, 2009). In other words HAART may inhibit or slow the progression of HIV and thus improve general functioning (Brown & Lourie, 2000). However HAART, unfortunately, does not completely eliminate HIV-associated neurocognitive disorders and there have been some investigations which have found little evidence to support the idea that HAART causes an improvement in cognitive functioning (Willen, 2006). The effects of HAART on cognitive functioning are not entirely clear, as there are often many other uncontrolled confounding factors that could account for an improvement or decline in cognitive functioning (Foley, Ettenhofer, Wright & Hinkin, 2008). It does seem, however, that HAART does slow the progression of HIV infection and it is unfortunate that is not widely available to the entire HIV-infected population, especially in developing countries such as South Africa.

Symptomatic and Asymptomatic HIV-infected children

HIV-infected children presenting with symptoms of HIV and low CD4 count should (if HAART is available to them) be put onto HAART as soon as possible. This is especially important with vertically infected symptomatic children, who, as noted above, may have more rapid and severe disease progression. These children would therefore need HAART to slow this progression (Bagenda et al., 2006). However, it has been recognized that there are a group of these children who are 'slow progressors' (Dunkley-Thompson et al., 2006, p. 295). These vertically HIV-infected children are also described as being asymptomatic; remaining immunologically and clinically stable for long periods of time after birth. These children will have a later onset of HIV associated symptomatology and have a stronger immune system than other more symptomatic HIV-infected children (Fundaro, Miccinesi, Baldieri, Genovese, Rendeli & Segni, 1998). In South Africa, for example, according to the *Guidelines for Antiretroviral therapy in children* (Cotton, Levin & Meyers, 2009) the status of asymptomatic is based on various factors. First, the child's clinical staging of HIV/AIDS is taken into account. These clinical stages range from stage one to stage four, with stage one showing no or few symptoms of HIV (asymptomatic stage) and stage four showing symptoms of unexplained severe malnutrition, recurrent severe bacterial infections and HIV encephalopathy among other physical impairments associated with this stage. Secondly, immunological factors such as CD4 count are taken into account and a child (who is older than five years) with a CD4 count above 350cells/µl, and who is still in the first or second clinical stage of HIV will be considered asymptomatic and remain HAART-naïve as a result.

Age is also taken into account. Currently, children who are younger than one year of age are immediately put onto HAART, while children older than five need to meet the above-mentioned criteria(this will be discussed in further detail as it applies to this study specifically in the methods section) (Cotton, Levin & Meyers, 2009). These children may only present with neuropsychological deficits in late childhood or early adolescence (Van Rie et al., 2007).

It is not entirely clear why some children remain asymptomatic, but there are suggestions that factors such as immunologic reactivity, education, environmental factors, lack of resources and even a different strain of HIV may play a role in the different rates of HIV progression (Bagenda et al., 2006). Nevertheless, this group of asymptomatic children represents a subgroup of HIV-infected children with a less progressive disease progression (Van Rie et al., 2007). Few studies have focused on the neuropsychological profiles of 'slow progressors,' especially those that remain HAART-naïve, and the precise presentations of the deficits seen are not entirely known (Armstrong, Seidel & Swales, 1993).

Social and environmental factors

There are various other social and environmental factors, as mentioned above, that are often not taken into account when considering HIV infection (Martin, Wolters & Toledo-Tamula, 2006). There is evidence to suggest that progression of HIV-infection in children is significantly related to social and environmental factors and not solely and directly related to the virus (Brown & Lourie, 2000).An extreme difficulty involved in understanding HIV infection in children is determining other factors that can play a part in the progression and presentation of HIV symptoms. These factors include (to name a few) low level of maternal literacy, poor socioeconomic conditions, poor quality of education and limited access to resources (Alvarez & Rathore, 2007). South Africa is a good example of a resource-limited country where neurological development may be greatly influenced by the environment in which the child lives (Meyers et al., 2007). Additional factors such as malnutrition and exposure to disease and toxins add to the likelihood that children will experience developmental delays or cognitive impairments over and above HIV infection (Armstrong et al., 1993).

Studies of the cognitive profiles of asymptomatic HAART-naïve children

Few studies in the field of the neuropsychology of HIV infection have focused on HAART-naïve children specifically. Even fewer studies have focused on the neuropsychological and behavioural profiles of HAART-naïve children (Bagenda et al., 2006). Participants in these studies, usually include both asymptomatic and symptomatic HIV-infected children, some of

whom had started HAART and others who were still HAART-naïve. Furthermore, control groups were not always used. For these reasons, the literature has not been entirely consistent with the findings reported.

Bagenda et al. (2006) investigated Ugandan children, aged 6-12 years, who were asymptomatic, vertically infected and who had never received any antiretroviral treatment. They compared those children to a control group of HIV-negative children. Although scoring slightly lower on academic achievement measures and showing more signs of acute illness and malnutrition, the infected HAART-naïve children still scored well within the average range on tests of neuropsychological function. These tests primarily included measures of sequential and simultaneous-processing and memory.

Another study of asymptomatic HIV-infected children showed relatively normal performances on tests of general intellectual functioning and language, however impairments in executive function were present (Bisiachhi, Suppiej & Laverda, 2000).

Koekkoek, de Sonnevilla, Wolfs, Licht and Geelen (2008) administered global intelligence tests as well as a series of neuropsychological tests to 22 vertically infected children. All the children were asymptomatic but only some were HAART-naïve. All the children scored in the average range compared to age appropriate norms on tests of general intellectual functioning, but cognitive domains of executive function, working memory and processing speed were seen as impaired. This study suggests that deficits in asymptomatic HAART-naïve children exist in specific cognitive domains. In the case of this study, the most severe impairment was seen in the domain of executive function.

A similar study (Blanchette, Lou Smith, King, Fernandes-Penny & Read 2002) supports these findings with the investigation of 14 children, only some of whom were asymptomatic. The children in this sample were administered a battery of neuropsychological tests and it was found that despite normal cognitive development, these children showed subtle motor impairments. The children's impairments were attributed to compromised executive functioning and slowed information processing. Additionally, Brown and Lourie, (2000) suggested the domain of language would most likely be impaired, even in asymptomatic HIV-infected children.

Finally, a group of eight children (ages 6-12) born with HIV and classified as asymptomatic, were investigated. The results of the neuropsychological tests administered suggested the presence of some learning disorders, as well as major memory and perceptual deficits (Fundaro et al., 1998).

The studies described above suggest that although asymptomatic HAART-naïve children may score in the average range on tests of general intellectual functioning, they may also show subtle deficits in several cognitive domains. The domains most likely to be impaired are executive function, memory, language, processing speed and motor function (Brown & Lourie, 2000). These outcomes suggests that despite a child being described as asymptomatic, HIV infection may still have an impact on certain aspects of the CNS, causing several deficits in certain cognitive domains (De Baets, Bulterys, Abrams, Kankassa & Pazvakavambwa, 2007). These findings underscore the importance of investigating specific cognitive domains in addition to general intellectual functioning. Asymptomatic children may have been classified as such due to their scores on global measures and the underlying deficits may, therefore, not be recognised

Longitudinal studies of the cognitive profiles of asymptomatic HAART-naïve children

Cross-sectional studies as discussed above may highlight particular cognitive deficits or behavioural difficulties, but they are unable to investigate how these difficulties may progress over time. It is suggested that with more focus on longitudinal follow-up studies, more comprehensive results will be acquired, and a pattern of cognitive development in asymptomatic HAART-naïve children can be more thoroughly investigated (Foley et al., 2008). A recognised limitation in this field of research is that this subset of asymptomatic HAART-naïve children is difficult to study, as children may progress rapidly into symptomatic HIV infection or will be put onto HAART despite being asymptomatic. With this being said, to my knowledge there are few relevant longitudinal studies that focus on asymptomatic HAART-naïve children specifically.

The exact impact of HIV on the developing brain is different in every child; there are ways to track the progression of HIV with various immunological markers. The most commonly used markers are measures of the CD4 count and the plasma viral load in the blood (Foley et al., 2008). Decreases in CD4 count, as the CD4 cells are the main target of the HIV virus, and increases in the plasma viral load, are typical immunological markers found in the blood of an HIV infected individual (Van Loon, 2009). Charlebois et al., (2010) found that these immunological markers may predict HIV disease progression in antiretroviral-naïve (ART-naïve) African children. Furthermore, researchers often suggest that clinical expression, as in the case of these immunological markers, may be correlated with cognitive functioning and CNS-related abnormities (Fundaro et al., 1998). For example,

the higher the CD4 count in an HIV-infected child, the less severe the CNS-related impairments.

In support of this, Ogunrin, Odiase & Ogunniyi (2007) observed that the occurrence of cognitive decline, such as psychomotor retardation and attention deficits, increased significantly, both in symptomatic and asymptomatic HIV infected individuals, who showed a decline in CD4 count. Therefore, it is suggested that when there is progressive immunosupression and disease progression in individuals, cognitive functioning may be negatively impacted. Cohen and Navia (2007) also suggested that the decline in HIV levels and high CD4 count are important factors in the stability and improvement of cognitive function.

In line with the above-mentioned studies, Walenda et al. (2008) investigated the general health of a group of asymptomatic HAART-naïve children and a group of symptomatic HAART-naïve children over a three year period. The results showed that after the three years, the mean CD4 count of the asymptomatic group had decreased, while 11% of the children in that group had died. 57% of the children in the symptomatic group had died over the three year period of the study, and the mean CD4 count was generally lower than in the asymptomatic group. This study suggests that, despite the asymptomatic status of the one group of children, immunosupression and deteriorating health were prevalent. Importantly, if cognitive functioning is correlated with immunological factors (Ogunrin et al., 2007), it is plausible to suggest that as health declines in individuals with both asymptomatic and symptomatic HIV, cognitive functioning may decline in these individuals as well.

Furthermore, Grubman et al. (1995) investigated children and adolescents living with HIV infection and who were vertically infected. 59.8% of the (42) children were asymptomatic at the start of the study, and, after 48 months, 23.8% of the children were still asymptomatic. Although there were children who remained asymptomatic, there was significant immunological deterioration and disease progression among these children. Based on the progression of symptoms and immunosupression seen in the group of children as a whole, the results of the study suggest that those who remained asymptomatic would soon follow a similar disease progression as those in more advanced stages of the disease. It was predicted that a follow-up study would show the continuation of this trend. These studies suggest that children with HIV, even asymptomatic HIV, may show health declines as they get older, and this decline in health may be associated with cognitive decline.

Other studies found in the literature, which focused on the neuropsychological performance of asymptomatic individuals over time, examined groups of adults. Bornstein,

Nasrallah, Para, Whitacre, Rosenberger and Fass (1993) investigated neuropsychological impairment in individuals at different stages of HIV infection. This study found that there were mild degrees of impairment across all the stages and disease severities, even in the asymptomatic group. It seems that with symptomatic individuals, neuropsychological impairment may be more severe, but there is evidence of some neuropsychological deterioration in asymptomatic individuals (Hall et al., 1996).

Although some research suggests that, over time, even asymptomatic children will show progressive cognitive decline, other research has found that changes in cognitive functioning over time may be difficult to detect in asymptomatic children. Thus, asymptomatic HIV-infected children may appear asymptomatic even though they may be experiencing subtle cognitive decline. For example, Franklin et al. (2005) investigated 39 vertically infected children (aged 2-12 years) over a 10 year period. 44% Of these children had asymptomatic HIV infection (as predicted by low viral loads) at first testing, and 56% of the children had symptomatic HIV infection. Major findings were: a significant decline in mental functioning in the first few years of life, but by age six, FSIQ scores in the low average range remained stable until age 12, without decline. Language scores were shown to decrease over time, while performance subtests showed improvement over time. Although IQ scores remained stable from age 6-12, an important finding in this study is that after the age of 3, developmental changes became more subtle and thus, harder to detect. Franklin et al. (2005) consequently suggested that IQ and cognitive scores may not always reflect these subtle changes.

Similarly, Gosling, Burns and Hirst (2004) studied 11 HIV infected children, some of whom showed little or no immunosupression over the course of the study (the time period is unknown). The majority of children scored within the average to above average range on cognitive tests. Four children did however deteriorate cognitively, but there was no specification as to which stage of HIV infection the children in this sample were in at the start of the study. Overall, there were no consistent patterns that emerged in terms of cognitive functioning. Gosling et al. (2004) explained these results by suggesting that each child has their own set of unique factors, such as environmental conditions and social support, that play a role in shaping development, and it is thus difficult to interpret development over time of the group as a whole. However, it is worth noting the possibility of more noticeable declines in cognitive functioning for children in the more advanced stages of HIV infection (Smith et al., 2006).

In summary, longitudinal studies of asymptomatic HAART-naïve children are scarce in the literature. This said; the most relevant studies seem to suggest that, over time, even asymptomatic children show decline in cognitive function as their health deteriorates. It is further suggested that this decline is inevitable and that it may be subtle and difficult to detect in earlier stages of disease progression. Additionally, the idea that unique factors may influence the functioning of each child may make cognitive functioning difficult to predict. These findings underscore the importance of investigating cognitive domains over a period of time in asymptomatic HAART-naïve children, to further understand their experience of the disease progression and the impact this experience has on cognitive functioning.

Studies of the behavioural profiles of HAART-naïve children

Research on the behavioural profiles of asymptomatic HAART-naïve children is limited. This may, in part, be attributable to the limited number of studies focused on asymptomatic HAART-naïve children, as children may rapidly become symptomatic and thus need to be part onto HAART. The literature concerning the behavioural profiles of asymptomatic HAART-naïve children may also be limited because it is very difficult for researchers to control for multiple factors, besides HIV-infection, that may impact upon emotional and behavioural functioning. Examples of these factors are poor nutrition, socioeconomic status and various other confounding factors which may cause a disturbance in emotional and behavioural functioning (as mentioned previously in this review) (Pearson et al., 2000).

Most African children with HIV are living in locations with limited resources where experience of trauma, life stressors and family problems are experienced on a daily basis (De Baets et al, 2007). This is especially the case for vertically infected children as they come from an HIV-infected family. It is therefore difficult to establish the causal relationship between HIV infection and behaviour (Mellins et al., 2003). Literature has shown, however, that HIV-infected children in general do commonly show more disruptive behaviour, particularly with regards to attention, concentration and emotional withdrawal (Brown & Lourie, 2000). In addition, HIV-infected children may also show more subjective distress than their peers and show additional symptoms of anxiety and depression (Brown & Lourie, 2000).

A study of clinically and immunologically stable HIV-infected children (previously treated asymptomatic children) showed that the children in that sample experienced more frequent behavioural problems as compared to age-appropriate norms. Although it has not been thoroughly investigated, the literature seems to suggest that HIV-infected asymptomatic

children will show behavioural outcomes consistent with those of symptomatic HIV-infected children – showing substantial difficulties in emotional and behavioural functioning (Nozyce et al., 2006). However, research of this nature is limited, and further research with specific focus on asymptomatic and HAART-naïve children is needed.

Longitudinal studies on the behavioural profiles of HAART-naïve children

The literature concerning the long-term behavioural profiles of HAART-naïve children is also limited. As mentioned already in this review, it is difficult to establish a casual relationship between HIV infection and behaviour and it may be increasingly difficult to establish this relationship over time (Mellins et al., 2003).

The longitudinal study (Gosling et al., 2004) mentioned above also investigated behavioural functioning in HIV-infected children over time. Although there was no clear pattern of results in terms of cognitive functioning, many behavioural and emotional difficulties were observed in this sample of children that were higher than the general population. It was also noted that although functioning was generally stable, some children had more severe difficulties than others. Importantly this study refers to the many environmental factors discussed above and suggests that each child's behavioural functioning is influenced by a variety of individual factors unique to their environmental and social living conditions.

Furthermore, as vertically infected children live with HIV their whole lives, this impact maybe significant. It is known that chronic childhood illness, such as HIV, has an indirect impact on behavioural functioning, due to the environmental and social stressors associated with the illness (Wallander & Thompson, 1995). Children are not only at risk for indirect behavioral problems, such as those associated with emotional withdrawal and subjective distress, but are also at risk for the direct impact that HIV has on the CNS in terms of regulation of emotion, behaviour and cognition (Brouwers, Moss, Wolters & Shmitt, 1994). Consequently, in the long-term it is suggested that these children will have increasing difficulty with behaviour and adjustment.

In summary, it seems that the most relevant literature suggests that over time, even asymptomatic children's health will decline and consequently their cognitive functioning will decline. In terms of behavioural functioning over time, it is suggested that because of the chronic nature of the disease and the effects of HIV both directly and indirectly on a child, behavioural difficulties will increase over time.

Conclusion

In conclusion this literature review has explored the impact of HIV infection in both symptomatic and asymptomatic HIV-infected children. The literature as a whole, concerned with the study of asymptomatic HAART-naïve children, has found inconsistent outcomes and investigation is most often approached using a cross-sectional study design (Foley et al., 2008). It is not entirely clear why HAART-naïve children have a slower disease progression, although explanations, such as a different strain of the virus, for example, have been suggested. However, despite being termed asymptomatic these children appear to have underlying impairments in certain cognitive domains. The cognitive domains that were suggested as showing impairment were the domains of executive function, memory, language, processing speed and motor function. Furthermore, these children may show average general intellectual functioning which often masks these subtle deficits.

It seems that the most relevant literature suggests that over time, even asymptomatic children's health will decline and consequently their cognitive functioning will decline. In terms of behavioural functioning over time, it is suggested that because of the chronic nature of the disease and the effects of HIV both directly and indirectly on a child, behavioural difficulties will increase over time.

RATIONALE FOR RESEARCH

The literature reviewed above suggests that there is limited and somewhat vague evidence regarding the neuropsychological and behavioural profiles of asymptomatic HAART-naïve children, as most of the reviewed studies did not investigate asymptomatic HAART-naïve children specifically. In addition, it seems that there are number of factors that may complicate the investigation of these profiles such as each child's unique environmental and social living conditions.

This study, which is divided into study 1 and study 2, focused on a group of pure asymptomatic HAART-naïve children, and is one of the first of its kind in South Africa. With access to this rare sample, study 1 and study 2 investigated both general intellectual functioning, as estimated by performance IQ (PIQ), as well as functioning in specific cognitive domains. Furthermore, this study also used a comprehensive battery of neuropsychological tests to investigate a full range of cognitive domains. This is important as many studies, only investigating general intellectual functioning, may not recognise underlying impairments in specific cognitive domains.

Furthermore, many studies in the above literature did not include a control group. Study 1, was able to compare the results of cognitive and behavioural assessment of asymptomatic HAART-naïve children to a healthy control group matched on as many demographic variables as possible. Study 2, was a longitudinal study and was able to investigate both behavioural and cognitive functioning of this sample of asymptomatic HAART-naïve children (included in study 1) over a period of 10-12 months. As seen from the literature, few longitudinal studies have been done for this sample of children.

Finally, children who are asymptomatic and HAART-naïve are difficult to access, as asymptomatic children may progress to symptomatic stages of the disease quite rapidly and can be put onto HAART. Therefore, both study 1 and 2 may contribute to the literature on HIV infection, specifically with regards to asymptomatic children, who are often not recognised as having cognitive and behavioural difficulties.

STUDY 1: A CROSS-SECTIONAL STUDY OF THE NEUROPSYCHOLOGICAL AND BEHAVIOURAL PROFILES OF HIV-INFECTED ASYMPTOMATIC HAART-NAÏVE CHILDREN

HIV infection is widely known for its effect on the human immune system; however one of the most serious consequences of HIV infection is its impact on CNS, thereby resulting in deficits in neuropsychological functioning. Children who are born with HIV are at the highest risk for experiencing cognitive deficits in early childhood, especially if they are symptomatic. Children who are referred to as asymptomatic do not experience typical symptoms of HIV and are consequently not treated with HAART. However, the impact that HIV has on their neuropsychology functioning is not widely researched. Furthermore, the impact of HIV on behaviour, for asymptomatic HAART-naïve children, is not widely researched.

It is unclear why HAART-naïve children have a slower disease progression, but it has been suggested that despite being asymptomatic these children have underlying impairment in certain cognitive domains as well behavioural difficulties. This cross-sectional study (study 1) investigated the neuropsychological and behavioural profiles of asymptomatic HAART-naïve children with comparison to a control group.

STUDY 1: RATIONALE

This research is part of a larger study that aims to correlate neuroimaging structural abnormalities, as detected by diffusion tensor imaging (DTI), of HIV-infected HAART-naïve children with their cognitive and behavioural profiles. Study 1, therefore may make a valuable contribute to further understanding of HAART-naïve children's neuropsychological and behavioural profiles within this larger study.

HIV infection is a serious public health problem, especially in South Africa. Therefore any further assistance in management in this field is a valuable contribution. This study may also aid in creating awareness of this population of asymptomatic HIV-infected children and will also help to inform the literature concerning asymptomatic children in terms of their behavioural and cognitive profiles. Findings from these investigations, and future studies built on these investigations, could contribute to the management of HIV-infected children and could inform educational and psychosocial interventions for both asymptomatic and symptomatic children (Martin et al., 2006).

As seen in the literature, many studies do not have participants that are exclusively HAART-naïve. Many of the participants were described as asymptomatic but had already

been started on HAART. For this reason, none of the reviewed studies have been able to effectively compare general intellectual functioning as well as cognitive functioning in specific cognitive domains for asymptomatic HAART-naïve children specifically. This kind of research would provide a more comprehensive picture of disease presentation in asymptomatic HIV-infected children.Furthermore, the behavioural profile of HAART-naive children has not been thoroughly explored thus far in the literature.

Finally this study investigated a sample of asymptomatic HAART-naïve children with comparison to a control group that was matched to the HAART-naïve children as closely as possible. With the use of a control group, some of the confounding factors discussed in the reviewed literature, can be better accounted for.

STUDY 1: SPECIFIC AIMS

The major aim of this study was to investigate the neuropsychological profiles of asymptomatic HAART-naïve children. The very limited research concerning this subset of children has found inconsistent findings. Therefore this study proposes the following aims:

1) To establish the neuropsychological profile of HAART-naïve children, using neuropsychological assessment of both general intellectual functioning (as estimated by PIQ) and functioning within specific cognitive domains, in comparison to a healthy control group matched on as many demographic variables as possible.
2) To study the behavioural profiles of HAART-naïve children, using behavioural assessment, in comparison to a healthy control group matched on as many variables as possible.

STUDY 1: HYPOTHESES

The hypotheses tested in this study, included the following.

1. Hypothesis 1: With regards to general intellectual functioning (using PIQ):

a) The HAART-naïve group will score within the low average PIQ range for children of this age.

b) The control groups will show PIQ scores within the average range but these will be higher than the HAART-naïve group (not significantly so).

2. Hypothesis 2: With regards to functioning in specific cognitive domains:

a) The HAART-naïve group will show subtle deficits on measures of memory, language, processing speed, motor function and executive functions as compared to the control group who will show no impairments in any of these cognitive domains.

3. Hypothesis 3**:** With regard to behavioural and emotional functioning:

a) HAART-naïve group will show substantial difficulty in behavioural and emotional assessment as compared to the control group.

STUDY 1: DESIGN AND METHODOLOGY

Design

This study was a quasi-experimental, cross-sectional, between-group comparison of cognitive and behavioural functioning in two groups: a HIV-infected HAART-naïve group, and a healthy matched control group.

This study received ethical approval from the University of Cape Town (ethics ref 299/2005, see Appendix A). Written informed consent and assent was obtained from the parent/caregiver of each participant (see Appendix B for example of these forms). Confidentiality was maintained throughout the study, with no risk of social physical or psychological harm to participants.

Participants

The HAART-naive sample included 12 children, aged 6 to 11 years, who were HIV-infected and HAART-naïve and whose parents provided informed consent for their participation. The investigators of the larger study decided upon this age group. This sample of children consisted of seven females and five males who were all from low socio-economic status backgrounds (see Table 1. on p. 30).Eleven of the twelve participants were Xhosa Speaking, and one participant was English speaking. The participants were recruited from an Isoniazid (INH) prophylaxis study of children with HIV at RXH, the Infectious Diseases Clinic at Red Cross Children's Hospital (RXH), and from Groote Schuur Hospital. These children had already completed a medical history and diagnostic examinations. Children on HAART or who have been on HAART previously were excluded from this group.

Any medical information, such as CD4% and whether each child was HAART-naïve or HAART-treated, was established by staff at RXH at the time of testing. These recommendations were established using three criteria: clinical stage (for example:

asymptomatic or symptomatic), immunological factors (CD4 count or percentage) and social circumstances (someone able to give the medication to the child). According to the staff at RXH, children older than 18months with a CD4 % less than 15 % were recommended for HAART. Children with a CD4 % larger than 15 % and with the consideration of their clinical and social circumstances were considered asymptomatic and were not recommended to start HAART. Clinical stages one and two, indicating fewer persistent symptoms of HIV, and CD4% greater than 15% were the inclusion criteria for children in this study who were considered asymptomatic and thus remained HAART-naïve refer to the explanation of these stages and criteria in the literature review, p. 6).

A group of 12 children who are HIV-negative served as a control group. These children were matched to the HAART-naïve group in terms of age, sex, language and (SES) (see Table 1.). Therefore 11 of the participants were fluent in Xhosa, and one child could speak English. These children came from similar residential areas as the HAART-naïve group in Cape Town, as control participants were recruited by snow-ball sampling. The HAART-naïve participants were able to assist us in this recruitment, by giving us the names and numbers of potential participants (to act as controls) in their communities. Contacted participants, who were appropriate matches to the HAART-naïve group, and willing to participate, further assisted us in contacting more control participants.

Materials and Measures

Each participant was assessed using a battery of neuropsychological tests designed to evaluate general intellectual functioning, as well as the specific cognitive domains of attention and processing speed, motor function, language, visual perception, memory, learning, and executive function. Parents or caregivers of the participants were asked to complete a behavioural assessment checklist. These measures were chosen as they assessed the cognitive domains relevant to the study of HIV infection and more broadly, to the study of childhood cognitive development. All instruments used were standardized, with good psychometric properties, and are commonly used in pediatric neuropsychology research and clinical assessment internationally.

Test instructions were translated into Xhosa. The translation process included a forward- and back-translation (authentication) where the translated test instructions were translated into English again. This was to ensure that there are no discrepancies between the original and translated instructions and that the instructions remained culturally suitable in the

Xhosa translation. The CBCL self-report questionnaire (to be discussed below) was the only measure that was not translated into Xhosa for this study.

A basic demographic questionnaire (see Appendix C) was given to each participant that required information about general demographic, obstetrics history, medical history, educational level and SES information. These questions were concerned with annual household income, for example number of rooms in the houses in which participants lived and the amenities in these houses.

SES was defined, with reference to Truter (2007), according to the following annual household income:

Low SES was defined as an annual household income of less than 50 000 per year. Medium SES was defined as annual household income of between R51 000-100 000 per year. High SES was defined as annual household income of 101 000 and above per year.

Neuropsychological Measures:

General Intellectual Functioning

General intellectual functioning (IQ) can be measured using the four subtests of the *Wechsler Abbreviated Scale of Intelligence (WASI*; Wechsler, 1999). Full Scale IQ is made up of the Block Design, Matrix Reasoning, Similarities and Vocabulary subtest. Verbal IQ (VIQ) is made up of the Similarities and Vocabulary subtests. PIQ is made up of the Block Design and Matrix Reasoning subtests.

This instrument was standardized and normed in the United States. According to the WASI administration and scoring manual, test-retest reliability coefficients range from 0.92 to 0.95 for both VIQ and PIQ. A systematic content analysis and a review of parallel items of similar subtests of other Wechsler batteries ensured content validity. Construct validity is supported by the intercorrelations of scores on the WASI subtests and other IQ tests and by the results of a factor analysis (Wechsler, 1999). Only one published South African study (Thornton et al., 2008) has used this measure and the Vocabulary subtest was substituted with the Human Science Research Council South African standardization of the Vocabulary test from the Wechsler Adult Intelligence Scale – 3rd version (WIAS-III, Wechsler, 1997). In some cross-cultural studies, PIQ is often viewed as a better estimate of general intellectual functioning as it does not rely on language abilities. Translations of the subtests of VIQ can be used, however translation of tests such as the Similarities and Vocabulary subtests can be problematic as concepts and meanings used in these tests may be difficult to convey in

another language (Mkoko, Vaughan, Wylie, Yelland & Jelsma, 2003). In this study, as all the participants were Xhosa speaking (except for one whom was English speaking); PIQ was used as an estimate of general intellectual functioning.

The following measures make up PIQ:
The *Block Design* subtest required the participant to replicate, within a time limit, modeled or printed 2D geometric patterns using two-colour cubes, thereby measuring perceptual organization. The *Matrix Reasoning* subtest measured non-verbal fluid reasoning. In this test the participant was required to indicate the missing piece from the choice of five possibilities to complete a series of incomplete grid patterns.

Attention, Tracking and Processing Speed

Three subtests from the *Wechsler Intelligence Scale for Children* (*WISC-IV*; Wechsler, 2003) were used to measure cognitive processes in this domain. Reliability for the WISC IV was examined by computing internal consistency values (split half correlations) or test-retest reliability. Some subscales dropped below .79, but 94% maintained .79 or better, with many increasing to .90 or better. Interscorer reliability by experts was generally .98, with Comprehension dipping to .95**.** Content Validity was established by reviewers and experts, as well as creating content similar to other, established tests to expand the evaluation base of the WISC IV.The *Coding (CD*) subtest measured speed of mental and graphomotor processing. The participant was required to copy, as quickly as possible within a time limit, symbols that are paired with either geometric shapes or numbers. The *Symbol Search (SS)* subtest was a relatively pure measure of processing speed. The participant was required to scan a group of symbols and then indicate whether a target symbol is present in that group. The participant completed as many of these items as possible within a specified time limit. The *Digit Span (DS)* test measured attention, concentration and working memory for verbal material. The participant was required to repeat a sequence of numbers in either the order in which they are orally presented by the examiner (*DS Forward*) or in the reverse order (*DS Backward*).

The *Colour trails test (CTT*; D'Elia, Satz, Uchiyama, & White, 1996) measured flexibility and switching. In the first part of the CTT the participant was instructed to draw lines between numbers scattered around a single sheet of paper, going from 1 to 2, 2 to 3, and so forth. The second part of the test was identical except that the two series of numbers were

presented on the page, each series in a different colour. The participant therefore had to join the numbers with alternative colours (for example: blue 1 to red 2, red 2 to blue 3, and so on).

Motor Functioning

The *Fingertip Tapping* subtest from the *NEPSY-II* (Korkman, Kirk, & Kemp, 1998) was used to measure self-directed manual motor speed. The NEPSY-II test developers report that reliability of the subtests of this battery was measured by means of inter-rater and interscores agreement, subtest internal consistency, and test-retest stability. The test's stability across time and age groups is supported by the range of stability coefficients from .62 to .89. The first task on this subtest required the child to make a circle with the tips of his/her thumb and index finger, opening and closing it as fast as he/she can until he/she makes 20 correct repetitions. The second part of the subtest required that the child tap his/her index fingertip, then middle fingertip, then ring fingertip, then little fingertip on the tip of their thumb, making a circle with each finger. The participant had to do this as fast as possible; the examiner recorded how long it took to complete five correct sequences. Participants always completed the tasks with the dominant hand before attempting the task with the non-dominant hand.

The *Grooved Pegboard Test* (Matthews & Klove, 1964) measured eye-hand coordination and motor speed. Participants were presented with a metal board with a matrix of 25 holes (in a 5 x 5 array) with randomly positioned slots, and with 25 pegs, each with a ridge along one side. The pegs were rotated to match the holes before they were inserted. The participant's task, then, was to insert the metal pegs into the slots as quickly as possible and in sequence. Children eight years or younger, were only required to complete the first two rows of pegs. The examiner recorded time to completion, first with the dominant hand and then with the non-dominant hand.

Language

The *Boston Naming Test – Short Form (BNT-2-SF4*; Mack, Freed, Williams, & Henderson, 1992) assessed the participant's visual confrontation naming ability. This test required the participant to look at black and white line drawings of common objects and name them. The names of the objects ranged in difficulty from simple, high frequency vocabulary words to rare words.

Visual Perception and Visuospatial abilities

The *Rey-Osterrieth Complex Figure* (*ROCF*; Rey, 1941) was a standardized measure of visual memory, visuo-constructional ability, as well as organization and planning. This test has been normed and standardized in many countries and for age groups ranging from 6 to 89 years (Mitrushina et al., 1999).This test is also used extensively in clinical neuropsychological practice in South Africa. The ROCF involved the copying of a two-dimensional image, changing pencil colours every 30 seconds. Once the copy was made, the card was removed from the participant's view, and the participants were asked to redraw the image from memory after a 3-minute delay. After a 30-minute delay, the participants were again asked to redraw the image from memory.

The scoring system used in this study was the Rey (1941) 36-point scoring system, which measured how accurately the participants were able to copy and recall the figure. According to this scoring system, 18 details of the figure were used to score the participants' drawings.

Learning and Memory

The immediate and delayed recall trials of the *ROCF* were used to measure visual perceptual and memory abilities of the participants. The administration of this test is described above.

The *Hopkins Verbal Learning Test (HVLT,* Brandt, 1991*)* assessed immediate memory span, new learning and new learning memory. In this test the experimenter read out a list of 15 nouns for four consecutive trails. The participant was then required to recall all the words after each trail.

Executive Functioning

The *NEPSY-II Inhibition* subtest was used to measure the inhibition of automatic responses. In this test the participant looked at a series of black and white shapes and arrows and named either the shape or direction or gave an alternate response, depending on the colour of the shape or arrow. The *Delis-Kaplan Executive Function System* (*D-KEFS*; Delis, Kaplan, & Kramer, 2001) measured key components of executive function. The D-KEFS is a standardized measure that has been normed for individuals between the ages of 8-89 years and has been shown to have a high content validity for the assessment of executive function. The Letter Fluency and Category Fluency subtests assessed fluent productivity in the verbal domain. For Verbal Fluency the participant was required to produce as many words that begin with a specified letter in one minute. Similarly, in category fluency, the participant was

required to produce as many possible words from a semantic category (for example: animals or fruit and vegetables) within one minute.

Measure of Behaviour

The *Child Behaviour Checklist (CBCL*; Achenbach & Resclora, 2001) required a parent (or caregiver) to rate the child's problem behaviours and competencies. This instrument was suitable for use in children aged 6-18 years. The scale developers report test-retest reliability coefficients of 0.95-1.00 and internal consistency reliability of 0.78-0.97.The first section of the CBCL consists of 20 items enquiring about the child's competence in various domains of functioning; the second section of 120 items enquires about the presence of behavioural and emotional problems. The two indices of the CBCL that are focused on in this study were Total Competence and Total Problems.

A score of less then 40 on the Total Competence index indicated that the child is in the borderline range and requires assistance with what should be age-appropriate activities. A score of less than 35 indicated clinical range for this scale. Within the Total Competence scale were three subscales that are categorized as Activities, School and Social. A score of less than 35 on any of these subscales indicated that children have borderline impaired functioning in that subscale and a score of less than 30 indicates clinical impairment.

For the Total Problems scale the outcomes of the parents' ratings were captured on three major scales: (1) Internalizing scale – indicates the presence of depression/withdrawal, anxiety and other somaticising behaviours; (2) Externalizing scale – indicates the presence of cruel, aggressive, or delinquent behaviours; (3) Total Problems scale - picks up on any other problem behaviours, such as immaturity or hyperactivity (Achenbach & Rescorla, 2001). A score between 60 and 65 on any of these scales indicated behaviours in a borderline range and a score of more than 65 indicates behaviours in a clinical range (see Appendix D, Table 14. for a table summarising these scores).

Procedure

A list of possible HAART-naïve participants for this study was identified by the administrators of the INH prophylaxis study in HIV children at RXH. After these potential participants were contacted and informed consent obtained from their parents/legal guardians, and assent was obtained from each child, a date and time for assessment was scheduled.

These assessments took place on weekday mornings, afternoons and weekends at the RXH HIV unit and Groote Schuur hospital. If it was convenient for the participants, a driver

was sent to their residential area to pick them up and bring them to the place of testing. The battery of neuropsychological tests was administered by a trained Xhosa translator. Each child's fatigue, effort, and motivation were monitored, and he/she was allowed to take breaks from testing where necessary. Children were accompanied by their parents or caregivers to the appointment, but those individuals remained in a separate room during the neuropsychological assessment.

The CBCL was administered to the parent while the child was completing the neuropsychological tests and as this test was not translated, the translator was required to assist the parent in this completion. If a child is, for any reason, was unable to continue with the assessment it was terminated immediately and an alternate time was scheduled. Each assessment session took between three to four hours. Tea, coffee, juice and biscuits were provided for the participants during the testing session and a Pick 'n Pay voucher and money were given to parents/caregiver to cover any travelling costs.

After the completion of the tests, if a parent/caregiver requested feedback about the assessment, a brief summary of the child's test scores was given to the parent/caregiver.

Similarly with the control group, once control participants were contacted (using snow-ball sampling as described above) consent and assent were obtained from both parent and child and assessments were scheduled. The same procedure as described above was implemented for the control group.

Data Analysis

Measures of central tendency (mean, median and mode) were calculated and histograms of normal distribution were obtained to detect any outliers. For all comparisons, effect sizes were calculated using a formulation elaborated from Aaron, Kromfrey and Ferron (1998) specifically used for small sample sizes.

The aim of this study was to compare the HAART-naïve group with the matched healthy control group. In order to do this, independent sample t-tests were used for comparison of each individual test across the groups. Assumptions of normality, homogeneity of variance and independence were assessed, before any test was performed, to ensure that they were upheld.

The Bonferroni correction method was used to protect against an inflated familywise error rate, due to the multiple comparisons that were done. This correction was done by dividing the statistical significance level α=0.05 by the number of t-tests performed (n=23).

Therefore the statistical significance level for the following statistical analyses was set to α=0.002.

STUDY 1: RESULTS

The HAART-naïve group (*n*=12) was closely matched to a healthy control group in terms of age, sex, language and socio-economic status. The summary of these variables for each group can be seen in Table 1. Independent sample t-tests were performed in this section, for comparison of each individual test between the two groups. The descriptive statistics and results of the statistical analyses are presented in table 2. When not otherwise specified, all assumptions for the statistical analyses were upheld.

Table 1

Demographic and clinical characteristics of the HAART-naïve group and the matched control group

Variable	HAART-naïve (*n*=12)	Control (n=12)
Age (months)	115.58(16.80)	115.42(15.01)
Sex (Female: Male)	7:5	7:5
Language (Xhosa: English: Afrikaans)	11:1:0	11:1:0
Handedness (R:L:X)	12:0:0	12:0:0
SES (low: medium: high)	12:0:0	12:0:0

Note. Age means are presented with standard deviations in parentheses. For handedness, R: L: X means ratio of right-to left-to cross-handedness. SES was determined by the socio-economic data obtained in the demographic questionnaires according to annual income.

Age

As seen in Table 1, the mean age of the HAART-naïve group, did not differ significantly from the mean age of the control group, $t(22)=0.03$, $p=0.98$, $d=0.01$; therefore the two groups were successfully matched on age.

RESULTS: Neuropsychological Functioning:

Table 2
Descriptive statistics and results for all neuropsychological tests administered

Outcome Measure	HAART-naïve (n=12)	Control (n=12)	*P*	*d*
General Intellectual Functioning				
WASI PIQ [b]	78.27(9.87)	80.33(10.15)	0.627	0.2
Executive Function				
D-KEFS Verbal Fluency [c]	14.60(4.48)	13.83(5.04)	0.713	0.15
D-KEFS Category Fluency [c]	15.40(4.25)	15.50(6.53)	0.652	0.19
NEPSY-II Naming [c]	3.10(50.63)	6.33(3.96)	0.048*	0.86
NEPSY-II Inhibition [c]	5.00(2.26)	7.42(2.11)	0.017*	1.07
NEPSY-II Switching [c]	3.50(2.32)	5.83(1.99)	0.019*	1.04
Language				
BNT-SF [a]	7.92(1.24)	6.92(1.51)	0.095	0.7
Attention and Processing Speed				
WISC Digit Span [b]	6.55(2.70)	6.00(1.21)	0.532	0.26
WISC Digit Span Forward [v]	7.09(3.45)	7.16(1.19)	0.944	0.42
WISC Digit Span Backward [b]	6.60(1.65)	5.92(1.31)	0.29	0.43
WISC Processing Speed [b]	11.18(4.67)	13.33(3.60)	0.227	0.5
Colour Trail 1 [b]	100.82(68.05)	86.83(31.04)	0.429	0.32
Colour Trail 2 [b]	220.64(68.05)	169.92(40.84)	0.039*	0.88
Motor Function				
Grooved Pegboard DH [c]	96.00(41.47)	74.08(31.89)	0.176	0.58
Grooved Pegboard NDH [c]	107.50(30.91)	94.08(49.84)	0.468	0.3
Fingertip Tapping DH [a]	9.08(2.64)	9.75(2.56)	0.537	0.25
Fingertip Tapping NDH [a]	8.00(2.00)	11.00(2.37)	0.003**	1.32
Visual Perception				
ROCF Copy [b]	20.09(6.22)	21.38(8.03)	0.675	0.17
Learning and Memory				
ROCF Recall [b]	39.64(8.71)	40.00(6.45)	0.909	0.05
ROCF Delay [b]	31.72(10.29)	37.92(7.97)	0.112	0.65
HVLT Total Score [b]	20.09(7.25)	15.08(5.02)	0.657	0.78

Notes: Means are presented with standard deviations in parentheses. DH refers to dominant hand. NDH refers to non-dominant hand.HVLT total score refers to the total number of words remember after three trials. [a] For this comparison, for the HAART-naïve group, n=12. [b] For this comparison, for the HAART-naïve group, n=11. [c] For this comparison, for the HAART-naïve group, n=10. *p<0.05, **p<0.01, ***Significant after Bonferroni correction p< .002. d=effect size.
All NEPSY (Inhibition and Fingertip Tapping tests) and WISC test scores (Processing Speed and Digit Span) are scaled scores. Verbal and Category fluency, BNT-SF, ROCF Copy, ROCF-OSS and HVLT total scores are raw scores. Grooved Pegboard and Colour Trails scores are completion times and ROCF Recall and Delay trials are T-scores.

General Intellectual Functioning

WASI

Performance IQ (PIQ) scores were used to estimate general intellectual functioning for both the HAART-naïve and control group. The control group performed better than the HAART-naïve group; however there was no statistically significant difference between the groups. According to qualitative description of WASI IQ scores (see Appendix E) the HAART-naïve group scored within the 'borderline' range for this test, while the control group scored within the 'low average' range for this test.

Executive Function

Verbal and Category Fluency

With regards to Verbal Fluency, the HAART-naïve group performed better than the control group. With regards to Category Fluency, the control group performed better than the HAART-naïve group. There were no statistically significant differences between the groups for either of these tests. In addition, the small effect sizes (d=0.15; d=0.19) respectively show that the differences between the groups were not substantial. For these tests, the HAART-naïve and control performed similarly.

Inhibition

Inhibition was scored using three tasks: Naming, Inhibition and Switching. Inhibition scores were converted into scaled scores for this comparison. For all three subtests, the control group did better than the HAART-naïve group. Using a significance level of α =0.05, the control group did significantly better than the HAART-naïve group on all three subtests. Taking the Bonferroni correction (α=0.002) into consideration, the differences between the groups on these three subtests were no longer significant. However, the effect sizes for all three subsets were substantially large, suggesting that with a larger sample size, the control group could have performed significantly better (according to α=0.002) than the HAART-naïve group. According to the qualitative description of NEPSY-II (Korkman et al., 2007) scaled scores (See Appendix F), the HAART-naïve group's performance was classified as 'well below expected level' (for Naming and Switching subtests) and 'below expected level' (for the Inhibition subtest). The control group's scores were classified as 'borderline' (for Naming and Inhibition subtests) and 'below expected level' (for the Switching subtest).

Language

Boston Naming Test (BNT-SF)

In order to assess the domain of language, the BNT-SF total scores (derived from uncued and phonemic cued answers) were compared across the two groups. For this measure, the HAART-naïve group performed marginally better than the control group. This was not a statistically significant difference, but this analysis had a large effect size (d=0.70).

Attention and Processing Speed

Digit Span

A total Digit span score was calculated by adding the score on the Digit Span Forward subtest with the score on the Digit Span Backward subtest for each group. For this measure, the HAART-naïve group did better than the control group; however there were no statistically significant differences between the scores. The small effect size, suggests that this difference was minimal. Looking at the Digit Span Forward subtest individually, the control group performed better than the HAART-naïve group, however for Digit Span Backwards subtest the control group performed worse than the HAART-naïve group.

Processing Speed

This measure was calculated by adding the WISC Coding scaled scores and the WISC Symbol Search scaled scores to get a measure of processing speed. Results from the independent t-test show that the control group performed better than the HAART-naïve group, however this difference was not statistically significant. The fairly large effect size (d=0.50) suggests that the difference between the groups was quite substantial, and with a larger sample size, this difference may have been significant.

Colour Trails 1 and 2

The scores for the Colour Trails 1 and 2 tests were recorded in seconds and represent the time it took the participants to complete each trail. The independent samples t-tests that were used to compare the groups showed that for both Colour Trails 1 and 2, the control group performed better (completed the trails more quickly) than the HAART-naïve group. Although there was no significant difference between the two groups on Colour Trail 1, the moderate effect size (d=0.32) suggests that there is a substantial difference between these groups and with a larger sample size, this may have been more apparent. In general the HAART-naïve group also tended to make more errors than the control group in this trail.

In terms of the Colour Trail 2 test, with statistical significance set at α= 0.05, there was a statistically significant difference between the two groups (the HAART-naïve group performed

more poorly than the control group) and the effect size was large. However, with the Bonferroni correction α= 0.002, the difference between these groups was not significant. It was also noted that the HAART-naïve group made more 'number errors' (errors in which the participant does not count upwards consecutively but may skip a number) than the control group.

Motor Function

Grooved Pegboard

The control group performed better than the HAART-naïve group on the Grooved Pegboard test, although this difference was not significant. The moderate effect sizes for both hands (dominant hand; d=0.58; non-dominant hand, d=0.30) suggest that with a larger sample size, this difference could become significant. As expected, the dominant hand time was faster than the non-dominant hand time for both groups.

Fingertip Tapping

Fingertip Tapping scores were converted into scaled scores for this comparison. For both dominant and non-dominant hand trials, the control group did better than the HAART-naïve group. However for the non-dominant hand, the control group did significantly better according to a significance level of α=0.01. However, when the corrected significance level of α=0.002 was applied; the difference between the two groups was no longer significant. According to the qualitative description of NEPSY scores (See Appendix F), the HAART-naïve group's performance was classified as being at the 'expected level' for this test. The control group's scores were also classified as at the 'expected level' (for the dominant hand trial) and as 'above expected level' (for the non-dominant hand trial).

Visual Perception

ROCF copy trials

These scores are raw scores based on the accuracy of the copied drawings. The control group performed better than the HAART-naïve group; however there was no significant difference between the groups. The small effect size (d=0.17) shows that this difference is not substantial.

Learning and Memory

ROCF Recall and Delay Trials

Scores for these tests were converted into T-scores according to the age of the participants.

For the Recall trial, the control group performed better than the HAART-naïve group; however there was no significant difference between the groups. Once again, the small effect size (*d*=0.17) shows that this difference is not substantial. For the Delayed trial the control group also did better than the HAART-naïve group. Although the difference was not statistically significant, the large effect size (*d*=0.65) shows that there is a substantial difference between these groups on this trial of the test.

HVLT

The HVLT total scores were calculated by adding the number of correctly remember words over three trials. It was found that HAART-naïve group remembered more words than the control group over these three trials. There was no significant difference, but the effect size (*d*=0.78) suggests that there was a substantial difference between the groups for this measure.

RESULTS: Behavioural Functioning

The following table describes the descriptive statistics for the scores on the CBCL scales for the HAART-naïve and control group. It also shows the differences between the groups (*p*) as well as effect size (*d*).

Table 3

Descriptive statistics for scores on the CBCL scales

	HAART-naïve (*n*=9)	Control (*n*=9)	*p*	*d*
Total Competence Scale	39.67(6.91) B	42.11 (5.51)	0.419	-0.37
Activities	39.38(7.17)	43.22(8.66)	0.338	-0.46
Social	48.00(7.48)	46.33 (6.20)	0.623	0.23
School	35.44 (8.83) B	42.11 (9.44)	0.141	-0.80
Total Problems	62.75 (8.17) C	63.00 (8.68) C	0.955	-0.03
Internalizing	66.38 (6.63) C	63.57 (4.93) B	0.376	0.45
Anxious/Depressed	57.88 (6.33)	60.43 (6.29)	0.449	-0.38
Withdrawn/Depressed	59.13 (8.97)	60.29 (5.09)	0.768	-0.15
Somatic Complaints	72.50 (6.91) C	64.71 (11.25)	0.125	0.80
Externalizing	58.38 (8.83)	59.29 (11.22)	0.863	-0.09
Rule-Breaking Behaviour	59.63 (6.46)	57.86 (8.15)	0.647	0.23
Aggressive Behaviour	57.88 (8.44)	62.00 (12.42)	0.460	-0.37

Notes. Means are presented with standard deviations in parentheses. B indicates a score in the borderline range. C indicates a score in the clinical range. Where there is no letter, normal range is indicated. Total Competence scale and subscale ranges are more severe the lower the

score. Total Problems, Internalizing and Externalizing Problems are more severe the higher the score. Refer to Appendix D for the break down of CBCL scores.

Scores in the above table were calculated using the appropriate CBCL/6-18 scales according to the sex of each participant. Each score is classified within a certain range, namely: normal, borderline clinical or clinical. These ranges indicate the severity of the behavioural problems seen in each participant. Each group's mean behavioural scores were calculated and these scores were given one of the above classifications. The two groups were then compared using independent sample t-tests. As seen from the table, there were no significant differences between the groups; however, in some cases the groups differed in terms of how they were classified.

Total Competence scale: School, Social and Activities

The Total Competence Scale is made up of three subscales, namely: Activities, Social and School. For this scale, the HAART-naive group was classified in the borderline range, while the control group was in the normal range, although there were no significant differences between the groups. Examining these subscales more closely, it is apparent that the HAART-naive group had more problems in both the Activities and School scales. The effect size (d=-0.46) seen for the Activities scale was moderate, indicating the potential for a significant difference between the groups if the sample size was increased. For the School scale, the HAART-naive group was classified as being in the borderline clinical range and control group was classified as being in the normal range. The effect size (d=0.80) indicates a substantial difference between the groups on this scale. For the Social Scale, the HAART-naive group had fewer problems than the control group and this difference was minimal.

Total Problems scale: Internalising and Externalising behaviours

As is clear from the table, both the control and HAART-naive group are classified in the clinical range for the Total Problems scale. The small effect size (d=-0.03) for this scale suggests that the two groups do not differ in terms of behavioural problems measured by this scale. Further, both groups showed more internalizing behaviours than externalizing behaviours, while internalizing behaviours were in the clinical range for the HAART-naive group and the borderline range for the control group. Looking more closely at specific internalizing behaviours, the control group showed more behavioural difficulties in terms of Anxious/Depressed and Withdrawn/Depressed behaviours, while the HAART-naive group showed more problems in terms of the Somatic complaints scale. In fact, the HAART-naive

group was classified in the clinical range for Somatic complaints, and the large effect size (*d*=0.80) suggests the HAART-naive group has substantially more problems than the control group in this regard. The small effect sizes seen for Withdrawn/Depressed scale (*d*=-0.15) and Anxious/Depressed scale (*d*=-0.38) suggest that the differences between the groups for these scales are negligible.

In terms of externalizing behaviours, the HAART-naïve group showed fewer difficulties in this area of behaviour than the control group, however there was no significant difference between the groups. Again, the small effect size suggests this difference is not substantial. The specific externalizing behaviour of Rule-breaking was seen more in the HAART-naive group; however, the small effect size seen for this scale suggests the two groups were quite similar in terms of this behaviour. For Aggressive behaviour, the control group had more problems as measured by this scale. Here the effect size is fairly small, again suggesting similar behaviour in both groups.

DISCUSSION

The primary aim of this study was to establish the neuropsychological and behavioural profiles of HIV-infected HAART-naive children, within the South African context. In doing so, this study aimed to investigate the effect that HIV infection may have on children who were classified as asymptomatic and therefore were not put onto HAART by comparing them to a matched HIV-negative control group on a range of neuropsychological tests and a behavioural measure. The following section will discuss these findings first in terms of general intellectual functioning and then in terms of specific cognitive domains. Finally, the results of the behavioural assessment will be discussed. It is to be noted throughout this section, that all these results were interpreted with caution given the small sample size of this study.

HYPOTHESIS 1: General Intellectual Functioning

Previous research within the field of paediatric HIV infection has shown varying results in terms of the general intellectual functioning of HAART-naïve children. In fact, most studies reviewed had a sample that did not consist purely of asymptomatic children, and when asymptomatic children were included, they were not always HAART-naive. This made the studies, and their findings, in this field difficult to interpret. However, it seems that the majority of studies reviewed found both asymptomatic and HAART-naïve children to score in the average to low average range on scores of general intellectual functioning (VIQ, PIQ and FSIQ), suggesting that intellectual functioning is relatively normal in these children (Koekkoek et al., 2008). However, research shows that these IQ scores are still lower when compared to a HIV-negative control group (Bagenda et al., 2006).

Based on these findings, the first hypothesis was that the HAART-naive group would score more poorly than the control group on a measure of general intellectual functioning (as measured by PIQ), but not significantly so. It was also predicted that these IQ scores would be in the low average range according to the qualitative description of WASI IQ scores.

The results of this study supported this hypothesis as the HAART-naïve group performed more poorly than the control group on the PIQ measure. Furthermore, there were no significant differences between the control group and the HAART-naïve group on these scores. According to a qualitative description of WASI IQ scores, PIQ scores fell within the borderline range (70-80) for the HAART-naïve group (which lies between the range of low average and below average) and in the low average range (80-90) for the control group.

Although the HAART-naïve group's scores fell within the borderline range, the small effect size present in the results suggests that the control group and HAART-naïve group performed similarly on this measure. These results are consistent with those reported by Bisacchi et al. (2000) and Cohen et al. (1991) who found that there was no significant difference in IQ scores between the HIV-infected group, consisting of asymptomatic children, and a HIV negative control group.

A possible explanation for this similarity is that before the actual onset of symptoms of HIV, asymptomatic children will exhibit subtle differences in neuropsychological functioning that may be difficult to detect. The subtle differences may have some effect on the CNS and more specific cognitive domains, but may have little effect on general intellectual functioning (Sirois & Hill, 1993). Without further investigation, the specific underlying impairments seen in specific cognitive domains may not be recognized (Martin et al., 2006).

Additionally, is important to note that both groups scored below the average range for PIQ scores. As both groups included children low SES backgrounds, the effects of this on the overall test outcomes need to be taken into account.

Gaylard (2005) investigated the IQ scores of people who spoke black African languages in South Africa in comparison to English speaking people. In this study, for all African language groups, PIQ scores were lower than VIQ scores. This type of study may suggest that African-based cultures, as seen in the current study, have different socio-cultural influences that impact upon their performance on certain tests. In South Africa, children (as in the current study) from low SES backgrounds are likely to be living in poor communities with little access to important resources. In line with this, socio-cultural and economic influence, such as poor quality of education, SES and schooling opportunities, may play a role in a child's development – how they process information, acquire abilities and use these abilities (Shuttleworth-Edwards et al., 2004). With this in mind, lack of exposure to physical resources such as building blocks, toys, and school resources, may contribute to the performance in terms of low PIQ. Children without this exposure may not have developed the relevant skills that would allow them to do well (within an average range) compared to American standards. Socio-cultural conditions may play a role in developmental delays and cognitive impairments, even in children without HIV infection (Alvarez & Rathore, 2007). This idea that socio-cultural factors may play a role in cognitive and behavioural development (Bagenda et al., 2006), in both groups of children, is an important factor to be mindful of throughout this discussion.

Why children remain asymptomatic or show slow progression of HIV-related symptoms is not clear, but this study supports a growing trend towards investigating general intellectual functioning as well as functioning of specific cognitive domains in order to gain a more comprehensive picture of HIV progression and its impact on neuropsychological functioning (Bagenda et al., 2006).

HYPOTHESIS 2: Cognitive Domains

Numerous studies have described impairments of specific cognitive domains in association with HIV infection(Brown & Lourie, 2000). The most commonly reported areas of impairment are memory, executive function, language, processing speed and motor function (Koekkoek et al., 2008). Thus, this is the basis of my second hypothesis, that specific cognitive domains may be impaired in these children. A further prediction was that the control group would do better than the HAART-naïve group in these domains.

Executive Functioning

Inhibition

The data obtained from the results of the NEPSY-II Inhibition measures, were consistent with previous literature (Bisiacchi et al., 2000; Blanchette et al., 2002: Koekkoek, 2008), as the HAART-naïve group did significantly worse than the control group on the three Inhibition subtests. The large effect sizes also indicate a substantial difference between these groups and possibly with a larger sample size, this difference may have been significant even when taking into account the Bonferroni correction used in this study. According to qualitative descriptions of NEPSY-II scaled scores (See Appendix F), the HAART-naïve group's scores were classified as 'below expected level' and 'well below expected level'. The control group's scores were classified as 'borderline' and 'below expected level'. Although the control group's scores were seemingly poor according to these classifications, it is important to note that the qualitative descriptions used were based on norms from an American population. Similarly to the discussion about PIQ and different socio-cultural and economic influences, these classifications may not be appropriate for this particular South African population. This is true of any qualitative descriptions referred to in the remainder of this study.

With regards to these results, it has been reported in the literature that in HIV infection, impairment in the domain of executive function occurs prior to even the expression of clinical symptoms of HIV (Sahakian et al., 1995). As age, gender and SES were as well

matched as possible, it may be reasonable to suggest that the significant difference in scores can be attributed to the effects of HIV on executive function. It is also suggested that although these children are seemingly asymptomatic; inhibition of automatic responses, monitoring and self-regulation, as measured by the Inhibition tests, all of which can affect optimal everyday functioning, may be compromised. This has important implications for the treatment of asymptomatic HIV-infected children who may remain HAART-naive because they have not presented with symptoms of HIV.

Verbal and Category Fluency

The scores on the Verbal Fluency and Category Fluency test for both groups suggest that the difference between the two groups on these measures was not substantial, and in fact, both groups did similarly on these measures.

According to previous studies (Bisiacchi et al., 2000; Koekkoek et al., 2008) it was expected that the HAART-naïve group would perform significantly worse than the control group on tasks that fell within the domain of executive function. This was supported by the current study as a significant difference (according to α =0.05) was seen between the control group and HAART-naïve group with regards to the Inhibition test (as discussed above). As the current study found minimal differences between the two groups on the Verbal Fluency and Category Fluency tests, it may be the case that the specific frontal lobe deficits predicted by the Verbal Fluency test are not characteristic of early stage asymptomatic infection (Bornstein, 1993).

With regard to the Verbal Fluency test within a South African context, there have been some efforts to develop letter sets appropriate for multilingual and multicultural South African children. It is usually the case that a Xhosa-speaking child will be administered the test in English or Afrikaans, depending on which language they feel more comfortable with. In the current study, it was noted that some children did say words in both Xhosa and English, while others did not. This could have been the reason of the inconsistent results seen between these two groups.

Language

Boston Naming Test (BNT-SF)

According to Brown and Lourie (2000), although a child may remain asymptomatic, they may show some language-related delays. However, other studies have found contrasting results (Bagenda et al., 2001, Bisiaccho et al., 2000; Blanchette et al., 2002) where language

abilities seemed to be spared in asymptomatic children, only some of whom were HAART-naïve. The results of this study support the latter, as the HAART-naïve group performed better than the control group on the Boston Naming Test, although not significantly so. The effect size is fairly large, suggesting there was quite a substantial difference between the groups.

It is suggested that in asymptomatic children, language impairment may not necessarily be an early predictor of cognitive impairment in this group of children; it may not yet be impaired. Bisiaccho et al. (2000) suggested that executive deficits were more appropriate indicators of cognitive problems, even when a child appears to be functioning normally. Although the above studies supported the current study's results in terms of language, it is not clear why the HAART-naïve group did better on this test than the control group.

A possible explanation of this may have to do with the use of the BNT-SF. It was noticed that throughout testing, certain pictures of objects (even pictures that were considered simple), were unknown to most children. Furthermore, children would often name pictures using a different Xhosa words than the one used on the BNT-SF scoring sheet. Although these words were different, they did still mean the same thing in Xhosa. In general, it seems that with translation of neuropsychological tests, there are some concepts or words than are difficulty to translate across language and culture (Mkoko et al., 2003). This highlights the difficult in the translations of English tests into African languages, and may have affected the results of this test.

Attention and Processing Speed

Processing Speed

The WISC-IV Coding and Symbol search tasks were used to assess processing speed for this study. The HAART-naïve group performed worse than the control group in terms of processing speed, but not significantly so. There was, however, a moderate effect size suggesting that this difference could tend towards significance with a larger sample size. Thus, some difficulties in terms of processing speed may be present. It may be the case that any impairment in processing speed was too subtle to detect with the tests used (Sirois &Hill, 1993). Additionally it may be the case that this domain may not yet be affected by HIV and may become more vulnerable as the children get older and more symptomatic.

Colour Trails

The Colour Trail 1 test measures perceptual tracking, sustained attention and graphomotor skills (D'Elia et al., 1996). This test is measured in terms of time (in seconds) and a faster time indicates a better performance on this test. For this test, the HAART-naive group performed more poorly than the control group, although not significantly so. The moderate effect size suggests that with a bigger sample size, this difference could have become more apparent.

Colour Trails 2 test measures all of the above mentioned skills as well as divided attention and sequencing skills (D'Elia et al., 1996). The HAART-naïve performed significantly more poorly (according to a significance level of 0.05) than the control group, suggesting that despite these children's' asymptomatic classification, that attentional and tracking deficits may be consequences of HIV infection. These data are consistent with those reported by Koekkoek et al. (2008) who found deficits in simple reaction time, attentional flexibility as well as pattern recognition, all of which was slower and less accurate in HIV-infected, asymptomatic children. Decline in attention is often recognized in children with symptomatic HIV-infection and it could be the case that the impairment in this domain for the HAART-naive group may decline further as the disease progresses (Wachsler-Felder & Golden, 2002).

Digit Span

The digit span test is primarily a test of attention. The Digit Span forward (DSF) test measures short-term memory, attention and concentration, while the Digit Span backwards (DSB) test measures working memory. Interestingly, the HAART-naïve group had a lower mean score for the DSF test than the control group but a higher mean score in terms of DSB. Overall, using the Digit Span total score, the HAART-naïve group performed better on this test than the control group, however this difference was not significant. The small sample size suggests that the difference between the groups on this measure was not substantial.

As mentioned above, an explanation of these results is that subtle cognitive deficits in working memory and attention domains are difficult to detect in this stage of disease progression (Sirois & Hill, 1993). According to Fundaro et al. (1998) memory impairment is usually detected in older children with HIV. This is not to say that HIV may not impact on the central nervous systems of these children, rather that symptoms have not yet been presented.

Motor Function

It was expected that in tests of motor function, the HAART-naïve group would show impaired performance compared to the control group (Blanchette et al., 2002; Da Baets et al., 2007). Blanchette et al. (2002) found that HIV-infected asymptomatic children performed poorly on measures of fine motor skills and strength. This was the case for both the Grooved Pegboard Test and Fingertip Tapping test. In this study, the control group did significantly better than the HAART-naïve group for the Fingertip Tapping test (non-dominant hand trial). The effect size of this measure was also large. A significant difference was not found between two groups with regards to the dominant hand trial, although the HAART-naïve grouped performed more poorly. These results are consistent with previous literature that suggests that motor functioning is compromised in the early development of HIV infection (Blanchette et al., 2002). According to Wachsler-Felder and Golden (2002) one of the most clearly recognized symptoms of paediatric HIV infection was deficits in motor function. In children who show symptomatic HIV, in the early years of disease progression, loss of motor milestones and difficulty in acquiring motor skills is a recognized symptom of HIV infection. It may be the case that this domain is particularly sensitive to HIV infection, even when the individual is asymptomatic.

Visual Perception, Learning and Memory

ROCF trials

The ROCF Copy trial is a measure of visual perception, planning and organisation. For this measure, the HAART-naïve group performed worse than the control group, however this difference was not significant and the effect size was small. This was in contrast to a previous study (Fundaro et al., 1998) that found asymptomatic children to show significant perception deficits. With regards to the Recall trial of the ROCF, the HAART-naive group performed worse than the control group, but the difference was minimal.

With regards to the ROCF Delayed trial, the HAART-naïve group again did worse than the control group, and although this was not a significant difference, the large effect size suggests that there is a substantial difference that may become significant with an increase in sample size. The HAART-naïve group may show a subtle impairment in long-term memory compared to the healthy control group.

A possible explanation for the results on the ROCF Copy and Recall trials (as mentioned before) is similar to an explanation already mentioned in this study. It may be the

case that subtle cognitive deficits measured by these two trials are difficult to detect. This study highlights the difficulty in differentiating asymptomatic individuals from healthy individuals as impairments present in cognitive functioning may not yet be detectable.

Another explanation for these results, as mentioned with PIQ, is that the children in this sample may not have had ready access to drawing materials or exposure to the abstract shapes seen in the ROCF. It was noted, that both the control and HAART-naïve group were slow in their completion of this trial and that often the pictures drawn were not accurate representations of the ROCF. On this note, this test was one of the last tests to be administered during the testing sessions. Although the children were given regular breaks when needed, the children in this sample could have tired during this stage of testing.

HVLT

The HVLT test assesses immediate memory span, new learning, and verbal memory. For the trials of this test, the HAART-naïve group performed better than the control group. These differences in performance were not significant, but a large effect size was present for HVLT total score (number of words recalled in three trials). It is not entirely clear why the HAART-naïve group performed better than the control group on this measure. These unexpected results could have been influenced by fatigue experienced by the participant, especially as this test has three trials. Furthermore, as should be considered for all the results in this study, the small sample size makes generalising results problematic and variability across the sample difficult to interpret.

General Discussion

The study of the neuropsychological profiles of HAART-naïve children is one of the first from a developing country such as South Africa. Despite being a study specific to South African children, the results suggest relatively normal PIQ (as compared to a control group) in asymptomatic HAART-naïve children. Importantly, although the HAART-naïve group performed similarly to the control group in terms of general intellectual functioning, further investigation is essential to recognise cognitive impairments that may be present in specific cognitive domains. This is of particular relevance in this study, as without further investigation, difficulties and impairments experienced by asymptomatic HIV-infected children may not be recognised. This study supports a growing trend towards investigating general intellectual functioning and functioning of specific cognitive domains in order to gain

a more comprehensive understanding of the impact of HIV on neuropsychological functioning in children.

The specific cognitive domains that were recognised as being impaired in the HAART-naïve group, or where this group performed significantly lower than the control group, were the domains of executive function (as measured by the Inhibition test), motor function (as measured by the Fingertip Tapping test) and attention and processing speed (as measured by the Colour Trails test). It was noted that not all the measures used to assess each of these domains showed significant impairment and it was thereby suggested that other impairments in these domains may be too subtle to detect at this stage of infection. Executive function, for example, is a set of cognitive abilities that also control and regulate other abilities. Therefore, specific deficits in this domain predicted by some tests of executive function (Inhibition) may not necessarily predict other deficits in this domain (Verbal Fluency). It may be the case that some aspects of this domain of functioning are more affected than others.

Furthermore, impairment in the cognitive domains of executive function, motor function, attention and processing speed fall in line with the structural abnormalities of the brain commonly seen in symptomatic HIV infection (see p. 7). Significant loss of neurons in the frontal cortex and subcortical damage, particularly seen in the basal ganglia, have been shown to contribute to impairment in these domains (executive function, motor function and attention and processing speed) in HIV-infected children (Hall et al., 1996). Thus, the performance on these tasks may be associated with cortical and subcortical atrophy, basal ganglia calcification and frontal lobe damage (brain abnormalities).

Additionally, a pertinent finding of this study was that differentiating asymptomatic children from normal children can be a difficult task that is complicated by the idea that deficits in some domains may only be detected at later stages of disease progression. For example, this study found that the HAART-naïve and control groups performed similarly on some tests (Digit Span and Category Fluency). It is possible that deficits in these areas may become more pronounced as these children get older and become more symptomatic, further research would be needed to establish this.

Further factors that have been touched on in the above discussion are that of environmental and social factors, that may influence these children's performance on these tests. This was shown in the results, as children in the control group also experienced difficulties with certain tests and in some cases performed more poorly than the HAART-naïve group. Interestingly, these environmental factors were experienced first hand by the

researchers during the administration of the translated tests. There were a few tests, noted throughout the testing sessions, which were met with unusual and unexpected behaviours from the children. For instance, the discontinue rule was met early for most children (in both groups) attempting the Block Design test and most children used a different name for the same picture in the BNT-SF. As mentioned earlier in this discussion, some concepts, ideas or words are not easily transferred across different languages and this may have accounted for these unexpected behaviours.

In summary, it can be seen from the above discussion that within the cognitive domains tested, the HAART-naïve group performed more poorly than the control group on many of the measures, in some cases significantly more poorly. Therefore, this study suggests that asymptomatic HAART-naïve children do experience underlying CNS impairment. Although these impairments may not be present in every cognitive domain, any impairment seen in these children are a cause for concern as asymptomatic children are typically not recognised as needing special services and management. There are many factors to take into consideration in this study, which make interpreting results difficult but it may be the case that children who are considered asymptomatic and who are HAART-naïve may in fact be vulnerable to the effects of HIV. Future research in this area is crucial for a more comprehensive account of these children's neuropsychological profiles and thereby appropriate management of these children.

HYPOTHESIS 3: Behavioural profiles

The body of literature dealing specifically with behavioural and emotional functioning of asymptomatic HAART-naïve children is extremely limited. According to this research, there are no studies that have investigated this sample specifically in terms of behavioural and emotional functioning. Noyzce et al. (2006) investigated 'clinically stable' HIV infected children, finding that these children had significant behavioural problems when compared to an uninfected group. There are some studies that have investigated behavioural and emotional functioning of symptomatic HIV infected children, most of which have found that; in general, these children do show more behavioural and emotional problems than HIV negative children (Brown & Lourie, 2000; Noyzce et al., 2006). With regards to HAART-naïve asymptomatic children, although they may not have to adhere to medication regimes and may not show typical symptoms of HIV, these children are still faced with living with this chronic illness. They may have to endure the same stigma attached to the disease, as well as face similar environmental and familial circumstances as symptomatic children. Therefore, it is

reasonable to suggest that they face similar challenges to symptomatic HIV-infected children and thereby may exhibit similar behavioural problems. In line with this, the third hypothesis predicted that the HAART-naïve group would show substantial behavioural difficulties; more so than the control group.

At the outset of this discussion, it is important to point out that behaviour can be affected by many different factors such as low SES, home and school environment and family support (to name a few). With specific reference to a South African context, these factors can be extreme. Thus, identifying HIV infection as an independent cause of behavioural difficulties is extremely difficult to do. Furthermore, the control group is susceptible to experiencing these factors as well (as they are matched to the HAART-naïve group and are classified as low SES participants), which may result in their experiencing problematic behaviours. Therefore, the direct impact of HIV on behaviour is not easily determined in this case of this study, even with the inclusion of a control group (Mellins et al., 2003). As seen from the results, there is some support for the hypothesis that the HAART-naïve group would show more behaviour difficulties than the control group, but there is also evidence of similar behavioural difficulties experienced by both groups. These results do not show a clear picture of behavioural functioning. Therefore, results of this study will be discussed and interpreted with caution and acknowledgment of the difficulty in studying behaviour in this population.

Total Competence

The results of the current study show some support for the hypothesis that the HAART-naïve group would show more behavioural difficulties than the control group. Although the difference between the groups was not statistically significant for any scale, the HAART-naive group was more often classified as being in the borderline and clinical ranges, while the control group was more often classified as being in the normal range. An example of this can be seen with the Total Competence scale, which showed the HAART-naive group to have behavioural problems in the borderline clinical range, while the control group showed normal behaviours. Specifically, the subscales of School and Activities showed the most substantial differences between the groups (according to effect sizes); with the HAART-naïve group showing more behavioural problems for both subscales. These behavioural difficulties as measured by the School scale, suggest that the HAART-naïve children may need additional support at school, are more likely to repeat grades and have more general problems at school.

Many children in the HAART-naïve group were reported as having had repeated a grade and needing extra help at school, more often than the control group.

These results are consistent with literature (Moss, Wolters, Brouers, Hendricks, and Pizzo, 1996), which found that children with HIV infection had many behaviour-related difficulties at school. These studies suggested that HIV infected children will not perform well at school, will neglect homework and have frequent absences from school. Mialky, Vagnoni and Rutstein (2001) found that more than half of the HIV infected children in their study required special services at school, and that 28% of the children repeated at least one grade. One explanation for these problems at school involves considering behavioural and emotional difficulties as indirect consequences of living with HIV (Wolters, Brouwers, Moss & Pizzo, 1995). This is supported by other literature, which has shown that living with a chronic illness such as HIV has a profound impact on children's emotional and behavioural development (Wallander & Thompson, 1995). HIV in particular has a negative stigma attached to it which may have a significant impact on emotion and behaviour of a child. Additionally, as seen in this study, all the HIV-infected children are from low SES communities, and the financial and familial struggles associated with this can have a profound impact on behavioural functioning (Rotheram-Borus, Murphy, Miller, & Draimin, 1997).

A second explanation for these problems with regard to school, are that behavioural difficulties are direct consequences of the HIV virus. In other words, these behavioural problems are a direct result of the impact that HIV progression has on a child's brain (Wolters et al., 1995). Neuropsychological functioning was discussed previously in this study, and it was shown that the HAART-naïve group did show some cognitive impairments. Although these children were not completely debilitated, it makes sense to postulate that some of these impairments (for example impairments in the domains of executive function and motor function, as seen in the above study) may also have an effect on school performance and the child's ability to manage school work and responsibilities as effectively as children without HIV infection.

Furthermore, with regards to the Activities and Social scales the HAART-naive group experienced more problems with regard to the Activities scale (participation in sports, chores and skills), but experienced fewer problems with regard to the Social scale (number of friends, participation in clubs/organisation, frequency of seeing friends and behaviours with others and alone). The difference was more substantial with regard to the Activities scale (*d*=-

0.46) but was not substantial with regards to the Social scale (*d*=0.23). The scores for the scales were all in the normal range.

Looking at the Social scale specifically, as mentioned above there are both direct and indirect consequences of HIV that may affect a child's behaviour. Additionally, factors associated with low SES backgrounds may further impact a child's behaviour. The fact that the HAART-naïve group showed less behavioural problems in terms of the Social scale was unexpected, but it can be understood by the many influential factors that may influence both the control group and HAART-naïve group in this sample (Moss, Bose, Wolters, & Brouwers, 1998). Similarly, Mellins et al. (2003) found that, when comparing the HIV infected with an HIV negative group, although finding high rates of emotional and behavioural problems, they failed to find an association between HIV disease and behavioural problems. These results may suggest that there are many other factors that influence behavioural problems in both HIV infected and HIV negative children.

Total Problems

The idea that there are many contributing factors faced by children in both groups is further emphasized by the fact that the HAART-naïve and control group were both in the clinical range for the Total Problems scale. This suggests that many HIV negative children may also exhibit behavioural problems, some of which may be quite serious. As mentioned above, although these children are considered a healthy control group, this does not mean that they are unaffected by problematic environmental and social factors that the HAART-naïve group may also experience. Essentially these mixed results reflect environmental and social factors that may be experienced by both groups. Some of these factors may include low SES backgrounds, quality of education, schooling opportunities, lack of financial and familial support and HIV infection in other members of the family. The unique circumstances in which both groups live could, very well, be the reason why the control group exhibited more behavioural problems than the HAART-naïve group on certain scales.

Internalizing behaviour

With regards to the internalizing behaviours scale, the HAART-naïve group was in the clinical range while the control group was in the borderline range. This suggests both groups have behavioural difficulties in terms of internalizing behaviours. Again this could be because of environmental and social factors. However, the HAART-naïve group did show more difficulties in terms of internalizing behaviours than the control group, and this could be

because of the additional stressors associated with living with HIV. These results are consistent with previous literature, which has reported internalizing behaviours such as anxiety, depression and somatic complaints to be present in HIV infected symptomatic children (Noyzce et al., 2006).

The internalizing behaviour that seemed to be most problematic was related to somatic complaints. In this study it was found that the Somatic Complaints Scale was in the clinical range for the HAART-naïve group. The commonly reported symptoms were headaches, nausea, skin problems, eye problems and body aches. In support of this, some studies report that HIV infected children will have a poorer quality of life (Mellins et al., 2003) in this case both physically and behaviourally. Somatic symptoms are often linked with depression and anxiety; however an alternative explanation is that these children may be showing physical symptoms of the HIV disease. As the HAART-naïve children have been classified according to CD4 % and presentation of symptoms, further investigation is necessary to explore the link between being asymptomatic children, their CD4 % and physical presentation of the disease during the asymptomatic stage.

For Anxious/Depressed and Withdrawn/Depressed Scale problems, both groups were in the normal range, but the control group experienced more difficulties, according to this scale, than the HAART-naive group. This could once again reflect the problems faced by healthy children in low SES communities; an alternative explanation is that children with HIV and their caregivers may exhibit a defensive adaptation style. In other words, mothers of children with HIV may be defensive about the HIV status of both themselves and their child and could thus underreport their psychological distress and the distress of their child. This type of case has been seen in other studies investigating chronic illness in children (Phipps & Srivastava, 1997). Another explanation revolves Child Behaviour Checklist, a self-report questionnaire that was not translated into Xhosa. Some of the mothers could have struggled to understand certain questions as abilities to speak and understand English was different in each mother. The researchers of this study attempted, to the best of their ability, to assist mothers as they filled out their forms. Despite this, some questions were left out, which made it difficult to get an overall picture of behavioural difficulties.

Externalizing Behaviour

What is clear however is that externalizing behaviours have been less frequently reported than internalizing behaviours, and for both the HAART-naïve and the control group, these scores were in the normal range. The more frequent occurrence of reports of internalizing

behaviours in the literature is consistent with the findings in this study, as all externalizing behaviours were in the normal range for both groups. These findings are consistent with the literature, in which more signs of emotional withdrawal, subjective distress and symptoms of anxiety and depression are seen in HIV infected children (Brown & Lourie, 2000). Bachanas, Kullgren, Schwartz, McDaniel, Smith & Nesheim (2001) have found that in situations where children born with HIV are living with a sick maternal figure, the child may be more anxious and worried about their parent. They may also start to think about the consequences of the disease and what this means for them in terms of their own health in the future. Children may often internalize these feelings, resulting in anxiety, depression and as seen in this study, possible somatic complaints. It was not established in the current study if the HIV-infected children knew of their HIV status.

In summary, these results show that although asymptomatic, these HAART-naïve children show similar behavioural problems to symptomatic HIV infected children. Although similar to the control group in some ways, internalizing behaviours, specifically somatic complaints, as well as problems with school performance, seemed more prevalent among the HAART-naive group than in the control group. The difficulty with studying this group of children is trying to understand the causal relationship between HIV and behaviour. As can be seen from the results and the above discussion, the control group face many problems of their own, and therefore it is not easy to link HIV directly to behavioural difficulties. An important issue to consider is that these children did not receive medication for HIV and were termed as asymptomatic. To many, this classification means they are healthy and consequently their behavioural functioning would not be considered. It is however important that their condition be taken into account so that appropriate services can be made available for these children.

Limitations and future directions

As mentioned throughout this study, this population of asymptomatic HAART-naïve children is often difficult to access. Due to this reason, this study had a small sample size that needs to be considered when interpreting the findings. Furthermore, environmental, social and economic factors were difficult to control for and these factors may have influenced both neuropsychological and behavioural outcomes. Future studies, for example, can aim to establish as many external factors (for both groups) that might influence the results in some way. A further limitation was in this study was the use of translations. This is a general problem in all South African studies attempting to investigate participants who may speak a

language that differs from the tests used, or to investigate a unique sample as seen in this study. Furthermore, the CBCL was not translated into Xhosa for this study and consequently many parents were unable to fill out this questionnaire themselves and only nine fully completed questionnaires were used in this study. Although the Xhosa translator was present to assist parents filling out the CBCL, it may have been difficult for the parents to answer some questions honestly and in detail. Future studies should consider translation of the CBCL self-report questionnaire.

Conclusion

This study of HAART-naïve asymptomatic children is one of few studies that have been able to include purely HAART-naïve children. Although there were many environmental, social and economic factors that may have played a role in some unexpected results, the results show that HAART-naïve children did show PIQ scores that were similar to a matched South African HIV-negative control group, as well as some signs of underlying CNS impairments. Although these impairments may not be present in every cognitive domain, it is an important concern as asymptomatic children are not typically recognised as needing special services and management.

In terms of behaviour, the HAART-naïve group did show similar behavioural problems to symptomatic HIV-infected children. Although similar to the control group in many ways, internalizing behaviours (somatic complaints) and school problems were problematic for this group of HAART-naïve children. A pertinent issue throughout this study was the consideration of environmental and social factors that may impact upon South African children from low SES backgrounds and how these factors might influence test performance, as well as cognitive and behavioural functioning.

Finally, asymptomatic HAART-naïve children may be seemingly healthy, but this research shows that the neuropsychological and behavioural functioning of these children needs to be more carefully considered. Consequently, the appropriate services can be made available to assist HIV-infected asymptomatic children (and their families) as they reach their adolescence. Further research is needed for a better understanding of HIV infection and disease progression and a more comprehensive understanding of the management necessary for asymptomatic HIV-infected HAART-naïve children.

STUDY 2: THE NEUROPSYCHOLOGICAL AND BEHAVIOURAL PROFILES OF HAART-NAÏVE CHILDREN: A FOLLOW-UP STUDY

The importance of investigating the cognitive and behavioural functioning of asymptomatic HAART-naïve children has been highlighted in study 1. However, cross-sectional studies are not able to capture the pattern of disease progression and development, specifically as experienced by asymptomatic HAART-naïve children. These kinds of studies may highlight particular cognitive deficits or behavioural difficulties, but they are unable to investigate how these difficulties may progress over time. It is suggested that with more focus on longitudinal follow-up studies, more comprehensive results will be acquired, and the pattern of cognitive development in asymptomatic HAART-naïve children can be more thoroughly investigated (Foley et al., 2008). Study 1 has highlighted the limited sources available in this area of research and this is also the case with any kind of follow-up or longitudinal studies. With this being said, study 2 investigated the neuropsychological and behavioural functioning of asymptomatic HAART-naïve children over a follow-up period of 10-12 months (after study 1).

STUDY 2: RATIONALE

The rationale for this study overlaps quite closely with the rationale presented in study 1, in terms of this sample of children being a unique subset of the HIV-infected population. This sample is, as mentioned, also difficult to access. Furthermore, few relevant studies have investigated this sample of children over a period of time.This kind of research could assist in establishing a pattern of cognitive and behavioural functioning over time, especially as it seems that many asymptomatic children will eventually become symptomatic. With this kind of information, the appropriate and necessary resources can be made available for these children during the appropriate stages of their disease progression

STUDY 2: SPECIFIC AIMS

The current study is a follow-up study of study 1, which aims to:

1) Investigate the neuropsychological functioning of the asymptomatic HAART-naïve children 10-12 months after their initial assessment (during study 1).
2) Investigate the behavioural functioning and profiles of the asymptomatic HAART-naïve children 10-12 months after their initial assessment (during study 1).

STUDY 2: HYPOTHESES

Hypothesis 4:

a) The asymptomatic HAART-naïve children will show a decline in cognitive functioning as compared to their previous cognitive outcomes in study 1.

Hypothesis 5:

a) The asymptomatic HAART-naïve children will show an increase in behavioural difficulties compared to their previous behavioural outcomes in study 1.

DESIGN AND METHODOLOGY

Design

This study was a longitudinal study investigating the behavioural and cognitive functioning of asymptomatic HAART-naïve children over a period of 10-12 months. The first testing sessions took place in 2009, and the follow-up testing sessions in 2010.

As in study 1, this study received extended ethical approval from the University of Cape Town to complete the 10-12 month follow up.

Participants

The sample included five children, ages 6-12 years, who were HIV-infected and HAART-naïve during the first testing session in 2009. These five children were part of study 1 and were therefore recruited from the Isoniazid (INH) prophylaxis study of children with HIV at RXH, the Infectious Diseases Clinic at RXH, and from Groote Schuur Hospital referred to before. The reason there are only five participants in this follow-up study out of a group of twelve was because from the time of initial testing (study 1), seven of the twelve participants were no longer contactable at the time this study took place. Their numbers were disconnected or unavailable. The attrition is an unfortunate consequence of longitudinal studies in general.

These children's parent or caregiver had signed consent to participate in this study in 2009 and, for the participants who were able to participant in 2010, signed consent to participate in this study again in 2010. As the focus of study 1 was specifically on HIV-

infected, asymptomatic HAART-naïve children, children on HAART or who had been on HAART previously were excluded from that sample. However, for study 2, the children that formed part of this follow-up study were included regardless of their HAART status, owing to the limited number of children that could be reached for study 2. The five participants were Xhosa-speaking, except for one participant who was fluent in English. As for study 1, the participants in this sample were all from low SES backgrounds.

Materials and Measures

Materials and measures used for study 2 were the same as those used in study 1 (refer to study 1, p. 21-26). These tests were translated into Xhosa for the purpose of study 1, and these same translated tests were used during study 2. In study 1, parents or caregivers of the participants were asked to complete the CBCL and during this study, this questionnaire was not translated into Xhosa. For the purposes of study 2, the CBCL was also translated (forward- and back-translation) into Xhosa.

Additionally, the same basic demographic questionnaires were given to the participant's parent/caregiver during study 2 (see Appendix C).

Procedure

As study 2 is a follow-up study of study 1, the same procedure was used in terms of making contact with participants, getting consent and assent, organising dates and time for the participants to come for testing, and testing procedure (refer to study 1, p. 26). The procedure of study 2 differed from that of study 1, in a sense that there was no control group needed for this study. A Xhosa translator also assisted in the administration of tests in this study.

Data Analysis

To investigate changes from T1 to T2 in neuropsychological test scores, the *Reliable Change Index* (*RCI*, Jacobson & Traux, 1991) is often employed. The RCI is typically used to detect if statistically significant differences in scores on neuropsychological tests administered at two different times are clinically meaningful. However for the purpose of this analysis, an extension of the RCI was used that takes practice effects into account (Parsons, Notebaert, Shields & Gukiewicz, 2009).

This RCI method is calculated using the following formula:

$((X_2 - X_1) - (M_2 - M_1))/SDD$

Were X_1 was the observed pre-test score, X_2 was the observed post-test score, SDD was the standard deviation of the group test-retest difference, M_1 was the group mean pre-test score, and M_2 was the group mean post-test score. Practice effect correction involves the addition of a constant that is based upon the group-level average change (Heaton et al., 2001; Woods et al., 2006).

Using the above calculation an RCI score greater than 1.64 indicates a significant change, while an RCI score less than 1.64 indicates a change that is not significant (1.64 equates to a 90% confidence interval).

STUDY 2: RESULTS

The primary purpose of this study was to investigate long-term neuropsychological and behavioural functioning of asymptomatic HAART-naïve children over a period of 10-12 months. As there were only five children in this study, each child's results will be presented as an individual case study. All five children were vertically infected with HIV and there was no report (by parents or relatives) of brain injuries or other illnesses. Any medical information, such as CD4 % and whether each child was HAART-naïve or HAART-treated, was established by staff at the RXH (refer to Study 1, p. 20-21).

Finally, some tests were not able to be completed by all participants due to time constraints as the testing sessions were sometimes longer than expected and the participant had to leave before the session could be completed.

Case 1- Name: SG

Date of Birth: 7 April 2001

Date of first testing session (T1): 7 July 2009 (aged 8 years 3 months)

Date of second testing session (T2): 18 June 2010 (aged 9 years 2 months)

SG is a Xhosa-speaking female who was in grade 3 at the time of T2 and had previously repeated grade 2. SG attended the first testing session with her grandmother and the second testing session with her biological mother. SG, her grandmother and mother were fluent in Xhosa. The medical records show that at T1, SG had a CD4% of 30.4 and she had not been put onto HAART. At the time of T2, SG had still not been put onto antiretroviral medication and was HAART-naïve.

Table 4

Case 1-SG: Behavioural Assessment

	T1	T2
Total Competence Scale	42	56
Activities	40	63
Social	48	58
School	46	32B
Total Problems Scale	41	64C

Internalizing	48	64C
Externalizing	34	54

Notes. B indicates a score in the borderline clinical range. C indicates a score in the clinical range. Where there is no letter, normal range is indicated. Total Competence scale and subscale ranges are more severe the lower the score. Total problems, Internalizing Problems and Externalizing Problems are more severe the higher the score. See Appendix D for further description of the CBCL scores.

Behavioural Assessment at T1

With regard to *behavioural problems* (See Table 1.), SG's grandmother completed the CBCL at T1. She reported that SG participated in sports and also has several hobbies. SG's grandmother reported her overall school performance to be in an average range. SG's Total Competence was reported as being in the normal range for parents' ratings of girls aged 6-11. Her scores on the Social, Activities and School scales were all in the normal range.

On the CBCL problem scales, SG's Total Problems, Internalizing and Externalizing scores were all in the normal age for girls her age. Although all these scales reported SG to be in the normal range, her grandmother did mention problems of anxiety and being fearful of certain animals, situations or places.

Behavioural Assessment at T2

At T2, SG's mother completed the CBCL. SG's mother reported that SG participated in sports and also had several hobbies. SG's mother also reported her overall school performance to be average. SG's Total Competence was reported as being in the normal range for parent's ratings of girls aged 6-11. However, although her scores were in the normal range for the Social and Activities scales, her scores on the School scale had declined since T2 (to the borderline clinical range).

On the CBCL problem scales, SG's Total Problems and Internalizing scores were both in the clinical range for girls aged 6-11 as compared to T1 where the scores were in the normal range. However, her externalizing score was in the normal range at T2. These results indicate that SG's biological mother reported more problems than are typically reported by parents of girls aged 6 -11 and more problems than reported by SG's grandmother at T1.

In summary, SG's problems at school seem to have increased and her Total Problems and Internalizing scores had declined since T1.

Table 5

Case 1:SG: Changes in Neuropsychological Test scores from T1 to T2

Measure	T1	T2
PIQ	84	83
DKEFS		
Letter Fluency [b]	13	13
Category Fluency [b]	12	13
BNT-SF [b]	6	5
WISC-IV		
Digit Span (total) [a]	5	4
Digit Span Forwards [a]	6	4
Digit Span Backwards [a]	6	5
Processing Speed [a]	14	13
Colour Trail 1 [c]	100	102
Colour Trail 2 [c]	220	295*
Grooved Pegboard DH [c]	48	108
Grooved Pegboard NDH [c]	68	106
Fingertip Tapping DH [a]	7	5
Fingertip Tapping NDH [a]	7	10
RCF		
Copy [b]	11.5	19
Recall [d]	30	51
Delay [d]	28	35
HVLT total score [b]	12	10

Note. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remember after three trials. [a] Scores on this test are scaled scores. [b] Scores on this test are raw scores. [c] Scores on this test are completion time in seconds. [d]Scores on this test are T-scores. *Indicates a significant change.

Changes in neuropsychological test scores from T1 to T2

The following section refers to the table 5. According to the RCI analysis, SG did show one significant change from T1 to T2, on the Colour Trails 2 test, RCI=1.73, where she completed this test significantly slower at T2 than at T1 (see Appendix G for full RCI analysis on all scores). Although other test scores may show an improvement or decline from T1 to T2, these changes are not indicative of meaningful improvement or decline.

With regard to SG's *general intellectual functioning* as measured by PIQ, this score was almost identical at T2.

With regard to *executive functioning*, SG performed similarly at both T1 and T2 for both Letter and Category Fluency. SG named one less semantic word than at T1, but performed the same in the Letter Fluency test at T2. Due to time constraints SG was unable to complete the Inhibition test.

With regard to *language*, SG did similarly on the BNT-SF at both sessions. Although SG had fewer uncued responses at T2, in general, she did know the answers to more items at T2.

With regard to *processing speed* (WISC Coding and Symbol Search subtests) and *attention* (total Digit Span), SG scored similarly at both T1 and T2. For the Colour Trails 1 and 2 tests, SG completed both trails in a slower time at T2.

With regard to *motor function*, SG showed a decline in the Fingertip Tapping score using her dominant hand at T2. However, SG did better at T2 when using her non-dominant hand. For the Grooved Pegboard test, SG completed both the dominant and non-dominant hand trials in a slower time at T2.

With regard to *visual perception,* SG performed better on the RCF copy at T2 than at T1.

With regard to *memory and learning*, SG did better on both the RCF delay and recall trials at T2. For the HVLT task, SG remembered fewer words in total at T2 than at T1.

In *summary*, SG's neuropsychological test performance did not differ significantly from T1 to T2 except on the Colour Trails 2 test where there was a significant decline in this score.

Case 2 – Name: KF

Date of Birth: 28 December 1998

Date of first testing session (T1): 28 July 2009 (aged 10 years 7 months)

Date of second testing session (T2): 14 June 2010 (aged 11 years 6 months)

KF is a Xhosa-speaking female who was in grade 4 at the time of T2 and had previously repeated grade 3. KF attended both testing sessions with her biological mother. KF and her mother were both fluent in Xhosa. The medical records show that in 2009, it was reported that KF was clinically well and attending school with a CD4% percentage of 30.7% and was therefore HAART-naïve. CD4% at T2 was unknown, but KF had been put onto HAART-treatment at the time of follow-up testing.

Table 6

Case 2-KF: Behavioural Assessment

	T1	T2
Total Competence Scale	30C	34C
Activities	28C	36
Social	50	48
School	32B	29C
Total Problems Scale	53	63B
Internalizing	63B	71C
Externalizing	47	57

Notes. B indicates a score in the borderline clinical range. C indicates a score in the clinical range. Where there is no letter, normal range is indicated. Total Competence scale and subscale ranges are more severe the lower the score. Total problems, Internalizing Problems and Externalizing Problems are more severe the higher the score. See Appendix D for further description of the CBCL scores.

Behavioural Assessment at T1

With regard to *behavioural problems* (see Table 3.), KF's mother completed the CBCL. At T1, KF's mother reported that KF did not participate in any sports and had few interests and hobbies. She also reported her overall school performance to be average. KF's Total Competence was reported as being in the clinical range for parents' rating of girls 6-11. KF was reported as being in the borderline clinical range for the School scale, and in the clinical range for the Activities scale.

On the CBCL problem scales, KF's Total Problems and Externalizing problems were in the normal range, while her Internalizing behaviours score was in the borderline clinical range. KF's mother reported more problems than typically reported by parents' of girls 6-11, particularly with regard to somatic and school complaints.

Behavioural Assessment at T2

At T2, KF's mother reported that KF's interest in hobbies had increased and that she viewed her daughter's performance in some subjects (art and social sciences) as average but that she was failing mathematics and science. KF's Total Competence was reported as being in the clinical range. Her scores on the Activities and Social scales were in the normal range, while

the School scale was in the clinical range. KF's Total Competence scale remained in the same range at T2, however scores in the School scale had declined to the clinical range.

On the CBCL problem scales, KF's total Problem score was in the borderline range, while her Externalizing problem behaviours remained in the normal range. KF's Internalizing problem behaviour score had declined and was in the clinical range. Again, this was with particular reference to somatic complaints which were reported as in the clinical range. At T2, KF's mother reported more Internalizing problems thatwas typically reported by parents' of girls 6-11.

In summary, KF was in the clinical range for the Total Competence scale at both T1 and T2, however, the School scale score had declined since T1. The Total Problems scale and Internalizing behaviours are shown to decline at T2 while Externalizing behaviours remained the same.

Table 7

Case 2:KF: Changes in Neuropsychological Test scores from T1 to T2

Test	T1	T2
PIQ	75	80
DKEFS		
Letter Fluency[a]	16	17
Category Fluency[a]	16	17
NEPSY-II		
Naming[a]	1	2
Inhibition[a]	3	5
Switching[a]	5	5
BNT-SF[a]	9	9
WISC-IV		
Digit Span (total)[a]	6	2
Digit Span Forwards[a]	5	4
Digit Span Backwards[a]	8	3
Processing Speed[a]	9	11
Colour Trail 1[c]	86	67
Colour Trail 2[c]	202	144
Grooved Pegboard DH[c]	94	77
Grooved Pegboard NDH[c]	104	99

Fingertip Tapping DH [a]	11	9
Fingertip Tapping NDH [a]	9	9
RCF		
Copy [b]	20	15.5
Recall [d]	46	35
Delay [d]	33	31
HVLT total score [b]	21	13

Note. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remember after three trials. [a] Scores on this test are scaled scores. [b] Scores on this test are raw scores. [c] Scores on this test are completion time in seconds. [d]Scores on this test are T-scores. *Indicates a significant change.

Changes in neuropsychological test scores from T1 to T2

The following section refers to the table 7. According to the RCI analysis, KF did not show any significant change on any of the tests from T1 to T2. This is important to note, as although test scores may show improvement or decline, these changes are not indicative of meaningful improvement or decline.

With regard to KF's *general intellectual functioning as measured by PIQ, this score* improved at T2.

With regard to *executive functioning*, KF performed similarly in both T1 and T2 in terms of Letter and Category Fluency. For the Inhibition test, KF showed an improvement on the Naming and Inhibition subtest and the same score on the Switching subtest at T2.

With regard to *language*, KF did similarly on the BNT-SF at both sessions.

With regard to *processing speed* (WISC Coding and Symbol Search subtests) KF showed an improvement in the score at T2. For *attention* (total Digit Span), KF showed a decline in this score at T2. For the Colour Trails 1 and 2 Test, KF did both trails in a faster time at T2.

With regard to *motor function*, KF, showed a decline in performance in the Fingertip Tapping using her dominant hand at T2. However, KF did better at T2 when using her non-dominant hand. For the Grooved Pegboard test, KF completed the test in a faster time with both her dominant and non-dominant hand.

With regard to *visual perception,* KF RCF copy score declined at T2.

With regard to *memory and learning*, KF showed a decline in both RCF delay and recall trials T2. For the HVLT task, KF remembered fewer words in total at T2 than at T1.

In *summary*, KF's neuropsychological test performance did not differ significantly from T1 to T2.

Case 3 – Name: EN

Date of Birth: 26 January 1999

Date of first testing session (T1): 29 June 2009 (aged 10 years 5 months)

Date of second testing session (T2): 25 June 2010 (aged 11 years 4 months)

EN is a Xhosa-speaking male who was in grade 4 at the time of T2 and had previously repeated grade 3. At both testing sessions, EN was accompanied by his biological mother. Both EN and his mother were fluent in Xhosa.

Without access to EN's medical records, there was no record of EN's CD4 % at either testing session. However, EN was reported as being HAART-naïve at T1, but HAART-treated at T2.

Table 8

Case 3-EN: Behavioural Assessment

	T1	T2
Total Competence Scale	50	39B
Activities	56	35B
Social	51	57
School	33B	27C
Total Problems Scale	---	79C
Internalizing	---	83C
Externalizing	---	78C

. *Notes.* B indicates a score in the borderline clinical range. C indicates a score in the clinical range. Where there is no letter, normal range is indicated. Total Competence scale and subscale ranges are more severe the lower the score. Total problems, Internalizing Problems and Externalizing Problems are more severe the higher the score. See Appendix D for further description of the CBCL scores.

Behavioural Assessment at T1

With regard to *behavioural problems* (See table 8.), EN's biological mother completed the CBCL. At T1 EN's mother reported that EN participated in two sports and that he was interested in three hobbies. She reported that EN had four or more close friends and that he

saw friends three or more times a week outside of regular school hours. EN's mother rated EN's school performance as below average in all subjects. EN's Total Competence score was in the normal range for parents' ratings of boys aged 6-11. His scores on the Activities and Social scales were both in the normal range, and his score on the School scale was in the borderline clinical range. Unfortunately, no further scales were calculated as too many items of the CBCL had not been completed by EN's mother.

Behavioural Assessment at T2

At T2, EN's mother reported that EN participated in three sports and that he had three hobbies. She reported that EN had four or more close friends and that he saw friends three or more times a week outside of regular school hours. EN's mother reported EN's school performance as average in language and science, but failing in social studies and mathematics. EN's Total Competence score was in the borderline clinical range for parents' ratings of boys aged 6-11. His score on the Activities scale was in the borderline clinical range, and his score on the Social scale was in the normal range. His score on the School scale was in the clinical range. EN's score on the Activities and School scale declined at T2.

On the CBCL problem scales, EN's Total Problems, Internalizing, and Externalizing scores were all in the clinical range for boys aged 6-11. These results indicate that EN's biological mother reported more problems at T2 than are typically reported by parents of boys aged 6 to 11.

In summary, EN's Total competence score showed a decline at T2, with Activities and School scales also showing a decline. The Social scale scores remained in the normal range at both T1 and T2.

Table 9

Case 3:EN: Changes in Neuropsychological Test scores from T1 to T2

Test	T1	T2
PIQ	70	70
BNT-SF [b]	9	7
WISC-IV		
Digit Span (total) [a]	2	4
Digit Span Forwards [a]	3	6
Digit Span Backwards [a]	5	4
Processing Speed [a]	4	7
Colour Trail 1 [c]	180	74
Colour Trail 2 [c]	300	263
Grooved Pegboard DH [c]	152	81
Grooved Pegboard NDH [c]	125	102
Fingertip Tapping DH [a]	6	9
Fingertip Tapping NDH [a]	7	6
RCF		
Copy [b]	12	23
Recall [d]	35	45
Delay [d]	23	37
HVLT total score [b]	23	24

Note. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remember after three trials. [a] Scores on this test are scaled scores. [b] Scores on this test are raw scores. [c] Scores on this test are completion time in seconds. [d]Scores on this test are T-scores. *Indicates a significant change.

Changes in neuropsychological test scores from T1 to T2

The following section refers to the table 9. According to the RCI analysis, EN did not show any significant change on any of the tests from T1 to T2. This is important to note, as although test scores may show improvement or decline, these changes are not indicative of meaningful improvement or decline.

With regard to EN's *general intellectual functioning as measured by PIQ*, this score remained the same at T2.

With regard to *executive functioning*, because EN had to leave the testing session early at T1, EN was unable to complete the Inhibition test, Letter and Category Fluency tests. With regard to *language*, EN showed a decline in BNT-SF at T2.

With regard to *processing speed* (WISC Coding and Symbol Search subtests) EN showed an improvement in the score at T2. For *attention* (total Digit Span), EN showed an improvement in this score at T2. For the Colour Trails 1 and 2 Test, EN completed both trails in a faster time at T2.

With regard to *motor function*, EN, showed an improvement in Fingertip Tapping scores using his dominant hand at T2. However, EN's performance declined at T2 when using his non-dominant hand. For the Grooved Pegboard test, EN completed the test in a faster time with both his dominant and non-dominant hand.

With regard to *visual perception,* EN showed an improvement in his RCF copy score at T2.

With regard to *memory and learning*, SG improved in both RCF delay and recall trials at T2. For the HVLT task, EN remembered one more word in T2 than T1.

In *summary*, EN's neuropsychological test performance did not differ significantly from T1 to T2.

Case 4 – Name: TD
Date of Birth: 20 November 2000
Date of first testing session (T1): 28 August 2009 (aged 8 years 9 months)
Date of second testing session (T2): 21 June 2010 (aged 9 years 7 months)

TD is an English-speaking female who was in grade 4 at the time of T2, and had not previously repeated a grade. TD attended both testing sessions with her biological mother and they were able to complete both testing sessions in English.

At the time of T1 she had a CD4% of 24.8%. Without access to medical records, TD's CD4 % is not known at T2. However she remained HAART-naïve from T1 to T2.

Table 10

Case 4-TD Behavioural Assessment

	T1	T2
Total Competence Scale	32C	51
Activities	37	47
Social	38	56
School	32B	38
Total Problems Scale	77C	75C
Internalizing	73C	63B
Externalizing	74C	75C

Notes. B indicates a score in the borderline clinical range. C indicates a score in the clinical range. Where there is no letter, normal range is indicated. Total Competence scale and subscale ranges are more severe the lower the score. Total problems, Internalizing Problems and Externalizing Problems are more severe the higher the score. See Appendix D for further description of the CBCL scores.

Behavioural Assessment at T1

With regard to *behaviour problems* (see Table 10.), TD's mother completed the CBCL. TD's mother reported that TD participated in three sports and that she had three hobbies. She reported that TD had one close friend and that she saw her friends once or twice per week outside of regular school hours. TD's mother rated TD's overall school performance as failing. TD's Total Competence score was in the clinical range for parents' ratings of girls aged 6-11. Her scores on the Activities and Social scales were both in the normal range, and her score on the School scale was in the borderline clinical range.

On the CBCL problem scales, TD's Total Problems, Internalizing, and Externalizing scores were all in the clinical range. These results indicate that TD's mother reported more problems than are typically reported by parents of girls aged 6-11.

Behavioural Assessment at T2

At T2, TD's mother reported that TD participated in three sports and that she had interests in three hobbies. She reported that TD had four or more close friends and that she saw friends one or two times a week outside of regular school hours. TD's mother rated TD's school performance as above average overall. TD's Total Competence score was in the normal range for parents' ratings of girls aged 6 to 11. Her scores on the Activities, Social, and School

scales were all in the normal range. It seems TD showed an improvement in her Social scale score at T2.

On the CBCL problem scales, TD's Total Problems and Externalizing scores were both in the clinical range for girls aged 6 to 11. Her Internalizing score was in the borderline clinical range. These results indicate that TD's mother reported more problems than are typically reported by parents of girls aged 6-11. TD's Internalizing scores improved from the clinical range to the borderline range at T2.

In summary, TD's Total Competence Scale score improved from the clinical range at T1, to the normal range at T2. The School Scale score also improved from the borderline clinical range to the normal range at T2. TD's Total Problems score remained in the clinical range at T2, while Internalizing behaviours improved from the clinical range to the borderline clinical range at T2. Externalizing behaviours remained in the clinical range at both T1 and T2.

Table 11

Case 4:TD: Changes in Neuropsychological Test scores from T1 to T2

Test	T1	T2
PIQ	80	85
DKEFS		
Letter Fluency [b]	17	20
Category Fluency [b]	17	19
NEPSY-II		
Naming [a]	3	2
Inhibition [a]	6	7
Switching [a]	7	5
BNT-SF [b]	8	8
WISC-IV		
Digit Span (total) [a]	7	7
Digit Span Forwards [a]	8	7
Digit Span Backwards [a]	7	7
Processing Speed [a]	12	13
Colour Trail 1 [c]	69	102
Colour Trail 2 [c]	193	151

Fingertip Tapping DH [a]	14	10
Fingertip Tapping NDH [a]	12	7
RCF		
Copy [b]	18.5	16.5
Recall [d]	45	49
Delay [d]	38	42
HVLT total score [b]	28	20

Note. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remember after three trials. [a] Scores on this test are scaled scores. [b] Scores on this test are raw scores. [c] Scores on this test are completion time in seconds.[d]Scores on this test are T-scores. *Indicates a significant change.

Changes in neuropsychological test scores from T1 to T2

The following section refers to the table 11. According to the RCI analysis, TD did not show any significant change on any of the tests from T1 to T2. This is important to note, as although test scores may show improvement or decline, these changes are not indicative of meaningful improvement or decline.

With regard to TD's *general intellectual functioning* as measured by PIQ, this score improved at T2.

With regard to *executive functioning*, TD showed an improvement in both Letter and Category Fluency scores at T2. For the test of Inhibition, TD showed an improvement on the Inhibition subtest, but a decline in score on the Naming and Switching subtests.

With regard to *language*, TD's scores on the BNT-SF remained the same at both sessions.

With regard to *processing speed* (WISC Coding and Symbol Search subtests) TD showed an improvement in the score at T2. For *attention* (total Digit Span), TD's score at both T1 and T2 were the same. For the Colour Trails 1 and 2 Test, TD completed both trails in a slower time at T2.

With regard to *motor function*, TD, showed decline in performance using both her non-dominant and dominant hand on the Fingertip Tapping test. For the Grooved Pegboard test, due to time constraints, TD was unable to complete this test at T1.

With regard to *visual perception,* TD showed a decline in the RCF copy score at T2.

With regard to *memory and learning*, TD improved in both the RCF delay and recall trials T2. For the HVLT task, TD remembered fewer words at T2 than T1.

In *summary*, TD's neuropsychological test performance did not differ significantly from T1 to T2.

Case 5 – Name: AX

Date of Birth: 18 June 1998

Date of first testing session (T1): 3 July 2009 (aged 11 years 1 month)

Date of second testing session (T2): 22 June 2010 (12 years)

AX is a Xhosa-speaking female who was in grade 6 at the time of T2 and had previously not repeated a grade. AX's biological mother attended both testing sessions. Both AX and her mother were fluent in Xhosa. Unfortunately, medical records for AX were not available at T1 and T2; however AX was reported as HAART-treated at the second session.

Table 12

Case 5-AX: Behavioural Assessment

	T1	T2
Total Competence Scale	39B	43
Activities	39	43
Social	44	47
School	46	46
Total Problems Scale	68C	58
Internalizing	73C	60B
Externalizing	54	49

Notes. B indicates a score in the borderline clinical range. C indicates a score in the clinical range. Where there is no letter, normal range is indicated. Total Competence scale and subscale ranges are more severe the lower the score. Total problems, Internalizing Problems and Externalizing Problems are more severe the higher the score. See Appendix D for further description of the CBCL scores.

Behavioural Assessment at T1

In terms of *behavioural functioning* (see Table 12.), at T1, AX's mother reported that AX participated in one sport and that she had two hobbies. AX's mother reported that AX had two or three close friends and that she saw friends three or more times a week outside of regular school hours. AX's biological mother rated AX's school performance as average overall. AX's Total Competence score was in the borderline clinical range for parents' ratings of girls aged 6 -11. Although her scores on the Activities, Social, and School scales were all in the normal range, their sum was low enough to produce a Total Competence score that was below the normal range.

On the CBCL problem scales, AX's Total Problems and Internalizing scores were both in the clinical range for girls aged 6 -11. Her Externalizing score was in the normal range. These results indicate that AX's mother reported more problems than are typically reported by parents of girls aged 6-11.

Behavioural Assessment at T2

At T2 AX's mother reported that AX participated in two sports and that she had two hobbies. She reported that AX had two or three close friends and that she saw friends three or more times per week outside of regular school hours. AX's mother rated AX's school performance as being in the average range overall. AX's Total Competence score was in the normal range for parents' ratings of girls aged 12 -18. Her scores on the Activities, Social, and School scales were all in the normal range. Total Competence score remained stable at T2.

On the CBCL problem scales, AX's Total Problems and Externalizing scores were both in the normal range for girls aged 12 -18. Her Internalizing score was in the borderline clinical range. These results indicate that AX's mother reported more problems than are typically reported by parents of girls' aged 12 -18. Total problems improved to the normal range, and Internalizing scores improved to the borderline clinical range from the clinical range.

In summary, AX's Total Competence scores improved from the borderline clinical range to the normal range at T2. Activities, Social and School scales remained in the normal range at T2. AX's Total Problem and Internalizing score improved at T2, while Externalizing problems remained in the normal range at T2.

Table 13

Case 5:AX: Changes in Neuropsychological Test scores from T1 to T2

Test	T1	T2
PIQ	65	65
DKEFS		
Letter Fluency[b]	14	9
Category Fluency[b]	24	19
NEPSY-II		
Naming[a]	1	6
Inhibition[a]	7	10

Switching [a]	1	3
BNT-SF [b]	9	6
WISC-IV		
Digit Span (total) [a]	7	5
Digit Span Forwards [a]	11	8
Digit Span Backwards [a]	5	4
Processing Speed [a]	7	10
Colour Trail 1 [c]	69	48
Colour Trail 2 [c]	156	135
Grooved Pegboard DH [c]	162	123
Grooved Pegboard NDH [c]	169	147
Fingertip Tapping DH [a]	6	3
Fingertip Tapping NDH [a]	6	9
RCF		
Copy [b]	16.5	11.5
Recall [d]	26	22
Delay [d]	21	20
HVLT total score [b]	31	30

Note. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remember after three trials.[a] Scores on this test are scaled scores. [b] Scores on this test are raw scores. [c] Scores on this test are completion time in seconds. [d]Scores on this test are T-scores. *Indicates a significant change.

Changes in neuropsychological test scores from T1 to T2

The following section refers to the table 13. According to the RCI analysis, AX did not show any significant change on any of the tests from T1 to T2. This is important to note, as although test scores may show improvement or decline, these changes are not indicative of meaningful improvement or decline.

With regard to AX's *general intellectual functioning* as measured by PIQ, this score remained the same at T2.

With regard to *executive functioning*, AX showed a decline in both Letter and Category Fluency scores at T2. For the subtests of Inhibition, AX showed an improvement on the three subtests.

With regard to *language*, AX's scores on the BNT-SF showed a decline at T2.

With regard to *processing speed* (WISC Coding and Symbol Search subtests) AX showed an improvement in the score at T2. For *attention* (total Digit Span), AX showed a decline in this score at T2. For the Colour Trails 1 and 2 Test, AX completed both trails in a faster time at T2.

With regard to *motor function*, AX, showed decline in performance with her dominant hand on this test, but an improvement using her non-dominant hand. For the Grooved Pegboard test, AX completed this test in a faster time than at T1 for both dominant and non-dominant hand.

With regard to *visual perception,* AX showed a decline in the RCF copy score at T2.

With regard to *memory and learning*, AX showed decline in both RCF delay and recall trials at T2. For the HVLT task, AX remembered fewer words at T2 than T1.

In summary, AX's neuropsychological test performance did not differ significantly from T1 to T2.

STUDY 2: DISCUSSION

The primary purpose of the present study was to investigate long-term neuropsychological and behavioural functioning of asymptomatic HAART-naïve children. Cross-sectional studies are important in this area of study; however they are not able to explore HIV disease progression over time and what effect the disease may have on neuropsychological and behavioural functioning. This study was designed to contribute to the literature on long-term neuropsychological and behavioural functioning of HIV-infected children HAART-naïve children, which, as has been noted, is not widely explored in current literature. The study includes a South African cohort specifically, for which there is an even greater dearth of research on this topic. The hypothesis put forward in this study, that HAART-naïve children will show a decline in both neuropsychological and behavioural functioning, will be discussed in the following section.

HYPOTHESIS 4: Cognitive functioning over time

The results of this study showed that the neuropsychological test performance of this group of HAART-naïve children did not significantly improve or decline over a follow-up period of 10-12 months. The five participants showed instances of both improvement and decline on the various cognitive tests, only one of which was significant (SG's performance on the Colour Trails 2 test), with no one test showing a pattern of improvement or decline for all five participants. In fact, some test scores remained the same at both T1 and T2 (for example: KF's performance on the BNT-SF and the Inhibition Switching subtest). While four out of the five participants did show minor improvement on the majority of tests, these improvements were not significant. If one looks closely at the one occurrence of significant change, where, according to the RCI analysis, participant SG showed significant decline on the Colour Trails 2 test, it is clear that this change is not consistent with a clear-cut model of improvement or decline for this participant. Overall, these results seem to indicate that this group of HAART-naïve children did not show a clear pattern of decline or improvement in any one cognitive domain over the 12 month follow up period.

The results of this study were contrary to the hypothesis put forward, namely that this group of children would show significant cognitive decline over time. This hypothesis was supported by various longitudinal studies, which have shown asymptomatic children to experience health deterioration over time, with many children becoming symptomatic during the course of these studies (Grubman et al., 1995; Walenda et al., 2008). With this in mind, it

was suggested that a decline in health was linked to progressive deterioration of cognitive functioning (Cohen & Navia, 2007; Ogunrin et al., 2007). Two of the children in the current study were put onto HAART by T2, indicating a decline in health, and thus it was further expected that these children would show cognitive decline. However, this was not the case in this study, as the only occurrence of significant decline was seen in a participant who was still HAART-naïve at T2 and whose other test scores showed no consistent pattern of decline or improvement. Similarly, the two participants, EN and AX, who were HAART-treated at T2, did not show any consistent pattern of improvement or decline (based on a limited sample). EN seemed to perform better on the majority of tests at T2, while AX showed more decline at T2. The effects of HAART on cognitive functioning are not entirely clear; however these effects were not under investigation in the current study. (Foley et al., 2008) Without further investigation and follow up of each child individually, it is difficult to suggest the reason for the one occurrence of significant change, especially as no other significant change in test scores were experienced by the rest of the participants.

With this in mind, the RCI analysis used in this study was specifically used to account for practice effects, as the follow up period until T2 was only 10-12 months. It was noted that there was some scores, especially with regards to the Colour Trails and Grooved Pegboard tests that seemed quite different, although they were not significant (for example: EN's faster completion time on the GPB DH at T2, and TD's faster completion time on the Colour Trails 2 test at T2). Not all the participants completed the Colour Trails and Grooved Pegboard tests were faster at T2. However, three out of the five participants did show faster completion on these tasks. It is suggested that practice effects may have played a role in these faster completion times, as well as familiarity and understanding of the two tests at T2.

While the findings of the current study did not support the original hypothesis, they are not unique. Gosling et al. (2004) found similar results in their study of 11 HIV infected children, some of whom were asymptomatic. In this study the majority of children showed no specific pattern of improvement or decline in the group. Gosling et al. (2004) suggested that the unclear pattern of results could be due to the difficulty in studying a group's development and cognition, primarily because each individual participant has their own set of unique factors that influence their improvement and decline. The difficulties involved become apparent when one appreciates that the participants who are HIV-infected and from low SES backgrounds, generally have quite volatile family lives and social conditions, which may mean that their unique factors vary to the extreme (Pearson et al., 2000). Factors such as the disease progression of each child, their current schooling, their family support system,

infected and deceased family members, as well as their individual understanding of the tests administered at each testing session, could affect the results. The problematic experiences associated with low SES, such as poor quality of education and impoverished living conditions, specific to this South African population, could be seen to exacerbate these factors and test scores. Similarly, in the current study, the mixed decline and improvement on difference tests for each participant could be a consequence of these unique factors that influence each child.

Extending on this, there is another factor besides environmental, social and economic factors that may play a role in individual test performance and could help to account for the unclear pattern of results. This factor of intra-individual variability can be defined as the difference in a child's development as compared to another child, as well as differences in a child's own cognitive performance over both long and short periods of time (Van Geert &Van Dijk, 2002). Siegler (1994) suggested that intra-individual variability allows children, at different stages of development, to employ different strategies when completing a task. The different strategies used can account for the fluctuations that can be seen in cognitive performance. These fluctuations could account for some children performing fairly well in a test in the first testing session, and then performing poorly in that same test in the second session and visa versa. In future studies concerning HIV, age-appropriate development and factors such as intra-individual variability could be more closely investigated, especially in studies of children.

With regard to general intellectual function, Franklin et al. (2005) found that from the ages 6-12, IQ scores remained stable over time in a group of both symptomatic and asymptomatic HIV-infected children. In the current study, the participants' mean ages were 9-10 years old, and, like the above study, PIQ scores at both T1 and T2 did not change significantly. Bagenda et al. 2006 found IQ scores to be in the average to low average range for school-aged children with HIV infection, and suggested that in general IQ scores may be spared throughout childhood, while impairment may be seen in other cognitive domains. Therefore, it may be the case that, while decline may or may not occur in other domains, IQ scores generally remain stable throughout childhood in asymptomatic children, as was the case in this study.

Another explanation for these results is that significant changes in cognitive performance may be too subtle to detect. Franklin et al. (2005) made the observation that after the age of three, developmental changes become more subtle and harder to detect in HIV-infected children. Consequently it was suggested that IQ and cognitive scores may not

always reflect these subtle changes. Therefore, another possibility to consider in terms of these results is that any cognitive changes that were present at the time of follow-up testing were too subtle to detect, over and above the influences of socio-economic and personal factors mentioned above, and possible practice effects. These types of changes may be detectable with more sensitive functional and structural imaging methods (Cohen & Navia, 2007). It is plausible that real changes were not detected in this study, hence follow up studies, aimed at investigating this possibility, could be conducted.

Additionally, if this sample of asymptomatic children are continuously experiencing subtle neuropsychological impairment (Hall et al., 1996), it is possible that noticeable declines in cognitive functioning may only start to develop in the more advanced stages of HIV infection or when this sample of children get older (as more symptomatic stages of HIV are associated with more rapid neurological impairment) (Smith et al., 2006). In other words, the incremental decline may only become observable at specific points in the disease progression, but the gradual worsening is not necessarily detectable during the asymptomatic phases. Grubman et al. (1995) found that the 23.8% of children who remained asymptomatic over the 48 months of their study, were younger than those who had a more advanced AIDS diagnosis. The mean age of the remaining asymptomatic children was 10, while the mean age of the children who had progressed to symptomatic HIV infection was 12. At this point in the current study, it is suggested that any cognitive changes that have occurred may not yet be detectable and will start to emerge with time. Grubman et al. (1995) suggested that progressive decline in health is inevitable for asymptomatic children, therefore further follow up studies, with a longer time frame, are needed to better understand disease progression.

Finally, it needs to be mentioned that this study had a small sample size of only 5 HAART-naïve children, two of whom became HAART-treated at T2. The effects of this treatment on cognitive functioning are not part of the scope of this study. Further investigation would be needed to understand what cognitive effect HAART treatment may have had on these two participants. With such a small sample size, it is difficult to generalise these results, as well as to find a distinct pattern of improvement or decline. Further studies with larger sample sizes, would be able to make stronger conclusions about cognitive functioning over time in these children.

In summary, although the results of the current study were not as hypothesised, it seems that in this particular group of HAART-naïve children, cognitive scores remained stable over 10-12 months. It may be the case that asymptomatic HAART-naïve children do show stable cognitive performance over time during childhood. However, it is possible that

the changes are too subtle for detection at this point in the study, and with age, these children may show more serous cognitive impairments. Individual factors for each child may also influence development, and a more extensive study would be needed to fully investigate cognitive performance over time.

HYPOTHESIS 5: Behavioural functioning over time

Literature dealing with long-term investigations of behavioural functioning of asymptomatic HAART-naïve children is limited, much like the studies investigating asymptomatic HAART-naïve children's behavioural functioning in general (as seen in study 1). The present study investigated the behavioural difficulties experienced by five asymptomatic HAART-naïve children over a 10-12 month period, using the CBCL. Although there were some changes in scores for the relevant scales, as with the long-term study of cognitive functioning, there was no overall pattern of increased or decreased behavioural difficulty.

Specifically, participants SG, KF and EN seemed to show more behavioural difficulties at the follow-up session, with regards to school related items and internalizing behaviours, while participants TD and AX seemed to show improved functioning in these areas. It is important to note however, that although TD and AX's internalizing behaviours seemed to improve in terms of their clinical classification (from clinical range to borderline clinical range) at T2, behaviours in these borderline clinical and clinical ranges are still considered problematic. With this in mind, it is suggested that despite these improvement for two participants, these children's behavioural functioning in terms of internalizing behaviours still remained problematic over the follow-up period. These findings are consistent with the literature, in which more signs of emotional withdrawal, subjective distress and symptoms of anxiety and depression are seen in HIV infected children (Brown &Lourie, 2000; Noyzce et al., 2006).

The increased behavioural difficulties experienced by SG, KF and EN (internalizing behaviours), were in line with the hypothesis that this group of children would show increased behavioural difficulty over time. It is suggested that, although these children are asymptomatic, having a chronic illness has a profound effect on them over time. It is possible that a child may decline in terms of their physical health, but being aware of their HIV status (as most of the children in this study were) may also have a significant emotional impact (Wallander & Thompson, 1995). As children with HIV reach adolescence, they may begin to think about and understand the consequences of having a chronic disease such as HIV, and the implication for their own health. Children may internalize these feelings as they get older,

possibly leading to a profound adverse effect on their behavioural functioning (Bachanas et al., 2001). Furthermore the virus can directly impact their CNS, impairing regulation of emotions and behaviour (Brouwers et al., 1994). It may be the case that, as the disease progresses, behaviour difficulties may increase; this could account for the increased difficulties seen in three of the five children in this study. Consequently, although these children are seen as asymptomatic, they could be in need of special services to help them with internalizing behaviours and school-related problems.

In a similar vein, different stages of disease progression may help explain the mixed results in terms of the School scale – behaviours which involve repeating grades, struggling at school and needing extra help. In terms of this scale, SG, KF and EN showed decline, while AX showed stable School scores in the normal range, with TD showing an improvement. Unfortunately, in the current study, actual immunological deterioration was not measured, but it might be the case that children further along in this progression worsened at school and with regards to school-related behaviours.

Although there are specific characteristics of HIV-infected children that may account for the changes in scores over time, a pertinent issue throughout this study is that there are several factors that may play a role in behavioural functioning. In the current study, the tested children all come from low SES backgrounds; it is thus likely that environmental stressors such as a lack of resources, impoverished living conditions and poor quality of education may play a significant role in their everyday lives and how they function. Another factor that may the influence HIV-infected children in this study, especially as they are vertically infected, is HIV infection of parental figures and other relatives. Similarly, children who are not infected with HIV may also have parents or relatives infected with HIV, and this could influence their behaviour in a way that is similar to the HIV-infected children in this study. Living with family members with chronic illness may also play a role in behavioural and emotional functioning.

As discussed above Gosling et al. (2004) investigated HIV-infected children's adaptive and behavioural functioning longitudinally, finding that although behavioural functioning remained stable, many behavioural and emotional difficulties were observed. These findings by Gosling et al. (2004) were consistent with the current study's findings, suggesting that individual factors may play a significant role in both the cognitive and behavioural outcomes of the child. Where one child's family life may have remained stable over 12 months, another may have lost a parent to HIV. Both these situations could influence the way a child was behaving at the second session. These individual factors may account for

why TD and AX's internalizing and school behaviours seemed to improved or remain stable at T2.

In line with this, as discussed briefly in study 1, is the problem of self-reported questionnaires. A parent of each child was asked to fill out the CBCL, relying on the parent's perceptions about their child's behaviour. A mother may have underreported distress in the child, while another, with a full-time profession, may not have been aware of any significant behavioural changes (Phipps & Strivasta, 1997). Problematically, the CBCL is an American measure, and although translated into Xhosa, some items may have been difficult to interpret. It would be most valuable to interview both parent and child in order to get an overall picture of behavioural functioning. In fact, interviewing and getting additional information from each child's teachers could also be useful. Interviews that take biological, social and psychological factors into account, of both mother and child, would be useful in future research.

In summary, some of the children in this study showed an increase in certain behavioural difficulties while others did not. This once again relates back to the idea that each individual child may have certain factors that influence their behaviour over time, making it difficult to isolate legitimate behavioural changes. Disease progression may also play a role in their behavioural development, and self-reported questionnaires may also be problematic. This study suggests that asymptomatic HAART-naïve children do show some behavioural difficulties, but difficulties experienced may not necessarily deteriorate or improve over time. The changes in functioning may be dependent on many factors, which differ for each individual child. This study, however, does show that behavioural functioning over time may deteriorate in some children; future, more targeted studies would be important for a better understanding of this development and the factors that contribute to or mitigate poor outcome. Although deemed asymptomatic, some children may benefit from intervention.

Limitations and future directions

As mentioned, the sample of children investigated in this study is a unique and rare population, thus contributing to the small sample size, of five participants for this study. However this small sample size does make it difficult to establish a clear pattern of results that may have become clearer with a larger sample size. If it is possible, future studies should attempt to investigate a larger sample size of asymptomatic HAART-naïve children. Furthermore, two of the participants in this study started HAART before the second testing session. The initiation of HAART could not be prevented in this study. The impact that HAART may have had on participants AX and EN, both emotionally and cognitively, was

not investigated, as this was not within the scope of this study. Future studies of this kind should take into account that some children may start HAART and should focus some attention on the implications of this. In line with this, this study was unable to provide a detailed account of CD4 counts and viral loads which may have shed some light on the results. As mentioned in the literature review, immunological factors are often correlated with cognitive decline or improvement, and further investigation into these factors would have provided a more comprehensive picture of these children's development. Future studies should include the investigation of immunological factors, and track how they decline or improve and how this related to cognitive and behavioural functioning

Furthermore, a general problem in cross-cultural neuropsychological testing is the administration of translated tests. The CBCL in particular was difficult for many parents to fill out, and the use of a Xhosa translator to assist with this process was crucial in this study.

Additionally, teacher's reports may also be helpful in future studies to get input on the child's behaviour at school. This may also help with issues of social desirability for mothers who want to make their child look good. Finally, as mentioned, many factors may play a role in the results of this study. Future studies should gather as much information about the participants (even in a control group) as possible, so that this additional information can be used to make links and further understanding in the research.

Conclusion

Longitudinal studies such as the current study are important for a more comprehensive understanding of neuropsychological and behavioural development in asymptomatic HAART-naïve children. An important factor that was highlighted in this study (and in study 1) was the idea that many uncontrollable factors, such as environmental factors, may play a role in each individual child's performance over time. This was the case for both cognitive and behavioural functioning. This is particularly relevant to a South African context, where environmental, social, financial and familial issues may vary to the extreme and have a significant impact on functioning as a whole. Other factors brought to light were that of cognitive changes in asymptomatic children being too subtle to detect or that they may only develop at later stages of disease progression. In terms of behaviour, three of the five participants did seem to experience some increase in behavioural difficulties over the follow-up period. Although it is difficult to attribute these changes to HIV, these results highlight that asymptomatic HIV-infected children may need additional services, despite their classification as asymptomatic. Future studies in this area will be crucial to a better

understanding of long term neuropsychological and behavioural functioning in asymptomatic HAART-naïve children. Finally, a pertinent issue throughout this study is that asymptomatic children are not unaffected by HIV. Through accessing a sample of HIV-infected, asymptomatic, HAART-naïve children, this research serves to demonstrate that this needs to be taken into account so that appropriate services can be made available for the proper care and management of these children.

STUDY 1 AND 2: FINAL CONCLUSIONS

In studies 1 and 2, the neuropsychological and behavioural profiles of a unique sample of asymptomatic HAART-naïve children were investigated, from both a cross-sectional and longitudinal perspective. These studies examined general intellectual functioning (as estimated by PIQ) as well as functioning in specific cognitive domains. A pertinent issue throughout this study, relevant for developing-work countries like South Africa, is that the unique environmental, social and socio-cultural factors experienced by low SES South African children has a significant influence on cognitive and behavioural functioning. Although these factors may have influenced the outcomes of this study, findings seem to suggest that there may be some signs of underlying impairments in the cognitive domains of executive function, motor function and attention. The non-specific pattern of long-term cognitive functioning in this sample of children may be attributed to difficulty in detecting significant change in this stage of the disease or a variety of other factors as mentioned above. The behavioural aspect of these studies suggested that this sample of asymptomatic HAART-naïve children seem to have difficulties in terms of internalizing and somatic problems; however, over time some participants showed an increase in these difficulties while others did not.

Although these results do not clearly support any one hypothesis, it seems that there are some signs of cognitive impairment and behavioural difficulties (some may be subtle). It may not be the case that these difficulties increase rapidly over time, as this study does not show this, but it seems that some consideration for these problems is needed. These and other similar studies, highlight the underlying pathophysiology in the CNS associated with HIV infection in children. Over and above the future directions discussed above, studies investigating the relationship between physical changes in the brain and neuropsychological and behavioural outcomes, (such as the larger study of which this current study forms a component) would contribute valuable findings to this area of research.

Finally, asymptomatic HAART-naïve children may not exhibit typical symptoms of HIV, but this study suggests that more attention should be paid to these children even without noticeable symptoms. If a child is classified as asymptomatic and HAART-naïve, any cognitive or behavioural difficulties may not be properly recognised and it is important that future studies investigate this unique subset of children so that they can be appropriately managed and cared for.

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APPENDIX A

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6492 • Facsimile [021] 406 6411
e-mail: Nosi.Tywabi@uct.ac.za

24 January 2008

REC REF: 299/2005

Prof H Zar
School of Child and Adolescent Health
Paediatric Medicine
Red Cross Hospital

Dear Prof Zar

PROJECT TITLE: EXTENDED FOLLOW-UP STUDY: LONG TERM STUDY OF 2 ISONIAZID (INH) PROPHYLACTIC REGIMENS WITH CONCOMITANT COTRIMOXAZOLE (CTX) IN HIV-INFECTED CHILDREN-IMPACT ON MORBIDITY, MORTALITY, BACTERIAL RESISTANCE AND INCIDENCE OF TUBERCULOSIS

Thank you for your letter to the Research Ethics Committee dated 21st January 2008.

Thank you for the progress report. We **approve** your request to extend the follow-up period for further two years.

Please note that we have closed the study: "strategies for prevention of opportunistic infections in HIV – infected South African children: comparison of 2 trimethoprin-sulphamethaxazole (TMP-SMX) prophylaxis regimens with and without concomitant isoniazid- impact on morbidity, mortality, bacterial resistance and incidence of tuberculosis"-Ref 057/2002. There has been some confusion between the two studies (original trial and long-term follow-up) in our files.

This study is **approved** to continue until 30 January 2009.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROF M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

APPENDIX B

PATIENT INFORMATION AND CONSENT FORM
CHILD ASSENT FORM
FOR THE STUDY

Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.

Sample: HIV Positive patients

Principal Investigator: Dr J Hoare

Dear Volunteer

You and your child are requested to participate in a medical research study that is being done at Red Cross Children's Hospital in the School of Child and Adolescent Health, University of Cape Town. The following describes the study and you and your child's role. Please take some time to read the information presented here carefully, and feel free to ask any questions.

Background
We are doing a study on how HIV affects children's learning and development. We want to compare tests of development (learning, memory, language and attention) and brain scans from children with HIV to children who do not have HIV.

If you are willing to allow your child to participate in this study, your child must be *HIV positive and currently not physically ill.*

HIV infection may cause slow development in a child. This can be either because of the virus itself or infections that the child may get. Even if a child seems well and is going to school, the HIV infection may affect some functions - like interfering with learning, with good memory, with doing mathematics, and with attention and behaviour.

We also want to learn about how caring for a child affects you as a parent. Parents, who have to care of a HIV-positive child, may experience more stress and difficulties than parents whose children do not have HIV. We want to compare test of parental stress of parents of children who are HIV-positive, to parents of children who are HIV-negative.

Purpose of the Study

The aim of this study is to measure tests of development (learning, memory, language, attention) and tests of behaviour and brain scans in healthy HIV-positive children and in healthy HIV negative children. The HIV-positive children's performance will be compared to the performance of healthy HIV-negative children. This will improve our understanding and management of children with HIV.

Procedures in the Study

Your involvement in the study will require you to visit the study doctor/team on three occasions at Red Cross Children's Hospital. This includes the brain scan, but this will be done at Tygerberg Hospital.

Confirmation of HIV diagnosis

If you are invited to participate in this study, it means that your child has *already been diagnoses as being HIV positive,* and has been referred to this study. Your child is unique in that he/she will have acquired the infection via mother to child transmission, and not via a blood transfusion or unhygienic needles.

Your child is currently attending a clinic for regular checkups. With your permission, we will contact the clinic which you and your child are attending to gain access to information in your clinic folders. During the course of your participation you will be asked certain medical questions regarding your child most recent CD4 count, viral load, and current treatment regime.

Brain scanning procedure

All brain scans will be done at a specialized facility at Tygerberg Hospital. A special brain scan (an MRI scan) will be done on your child – this examination is not harmful and it is not painful. Your child will be asked to lie still on a special bed while the scanner takes the pictures of your child's head - this will be for a maximum of 30 minutes. Some children may find the machine a bit scary. If your child is very anxious or scared or unable to lie still for that long, we will not continue with the examination.

Neurological examination

You child will be required to undergo a neurological examination which will be performed by a study doctor. The purpose of this examination is to check that your child's sensory and motor responses, and also their reflexes, are functioning properly and that there is no damage to their nervous system. To test this, the doctor will ask your child to do a series of playful activities, for example touching their nose or their ankles. These tasks are not harmful to your child. If your child is anxious, you may accompany him/her in the examination room.

Procedure for drawing of bloods

This part of the study involves the long-term storage of DNA (genetic) taken from a sample of your child's blood for future analysis.Genetic material, also called DNA, can be obtained from small samples of blood.Previous studies have shown that HIV infection can have

damaging effects on the brain. We are however unsure as to how serious these effects may be in young children. In this part of the study, we hope one day to be able to use genetic material, such as we will be collecting, to assist us in identifying genes that will tell is what people may be particularly vulnerable to experience harmful effects, and what genetic patterns are likely to make people more susceptible to becoming infected with the HIV virus.Before the brain scan is done, a registered nurse will draw a small amount of blood from your child. This procedure will not be harmful to your child. Your child may feel a light prick when the needle is inserted into his/her arm, but will not experience any pain.The needle is connected to a thin plastic pipe and the blood then flows into a small blood sample tube. The test will require about 1 teaspoon of blood, and is performed only once.

Your blood will only be used for genetic research that is directly related to this study looking and diffusion tensor in HIV-infected children. Also if the researchers wish to use your stored blood for *additional research in this field* they will be required to apply for permission to do so from the Human Research Ethics Committee at UCT. If you do not wish your blood specimen to be stored after this research study is completed you will have an opportunity to request that it be discarded when you sign this consent form.

Your Part in the Study

While your child is being tested by members of the study team, you will also be asked to completed questions by another member of the study. You will complete a general demographics form, and other psychological tests pertaining to your child's mental health and yours. These tests are not harmful, but may ask some sensitive questions about your life. Our researchers will do all they can to emotionally support you while you complete these forms. It is important for us that you answer these questions truthfully, so that we can better understand you as a parent, and your needs.

A psychologist will interview your child either at school or at clinic. Your child will then be given one extra appointment to go Tygerberg hospital, on a day that is convenient for you, where the brain scan will be done. Transport money and food vouchers will be provided for you and your child for these visits.

Risks to You and Your Child

There are only low or minimal risks associated with your participation in this study. If you feel tired at any point during any of the visits, you should please ask your study doctor/psychologist for a rest. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessments at another time.

There are no direct risks in having blood taken for genetic testing.

Furthermore, there are no known risks for your child for either the psychological tests or the brain scan. The brain scan does not involve any radiation.

Benefits toYou and Your Child
Although there is no direct benefit for you or your child, the results of this research may help to inform us to what the common school and behaviour problems are that healthy HIV-positive childrencan have. This will help us to decide if we need to consider extra treatments for these children.

Confidentiality
You and your child's test results will be kept confidential (private) and will only be used by the members of this study for the purpose of research. If any information from this study gets published, we will make sure that your personal details will remain confidential at all times.

This study has been approved by the Committee for Human Research of the University of Cape Town (UCT). It will be conducted according to Medical Research Council guidelines on good clinical practice (2003) as well as the Declaration of Helsinki Guidelines (Edinburgh, 2000), which provide detailed guidelines that relate to the ethical conduct of studies involving human subjects.

Voluntary Participation
You and your child's participation are entirely voluntary. You or yourchild is not under any obligation to participate. If you choose not to allow your child to participate, it will not affect you or your child negatively or prevent your right to future health care services. You have the right to withdraw your child from the study at any time.

You have the right to ask questions at any time about any aspect of the study. If you have any queries, you can contact Jackie Hoare on 021 4042134/2164

You are entitled to a signed copy of this document.

If you agree to take part, please complete the following section:

ASSENT OF MINOR

I (*Name of Child/Minor*) _____have been invited to take part in the above research project entitled**: Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.**

The study doctor/nurse and my parents have explained the details of the study to me and I understand what they have said to me.

- They have also explained that this study will involve 3 assessments which include interviews, filling questionnaires, a physical examination, blood sampling, and a brain scan.
- I also know that I am free to withdraw from the study at any time if I am unhappy.

- By writing my name below, I voluntarily agree to take part in this research project. I confirm that I have not been forced either by my parents or doctor to take part.

_____

Name of child **(To be written by the child if possible)**

DECLARATION BY PARENT/LEGAL GUARDIAN

By signing below, I *(name of parent/legal guardian)*
_____ agree to allow my child (*name of child*)
_____who is ___ years old, to take part in a research study entitled: **Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.**

I declare that:

- I have read or had read to me this information and consent form and that it is written in a language with which I am fluent and comfortable.
- If my child is older then 7 years, he/she must agree to take part in the study and his/her ASSENT must be recorded on this form.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to let my child take part.
- I may choose to withdraw my child from the study at any time and my child will not be penalised or prejudiced in any way.
- My child may be asked to leave the study before it has finished if the study doctor or researcher feels it is in my child's best interests, or if my child does not follow the study plan as agreed to.

☐ I agree that my child's blood sample can be stored, but I can choose to request at any time that my stored sample be destroyed. I have the right to receive confirmation that my request has been carried out.

OR

☐ Please destroy my blood sample as soon as the current research project has been completed. **(Tick the option you choose**)

Signed at (*place*) _____on (*date*) _____20____

_____

Signature of parent/legal guardian

DECLARATION BY INVESTIGATOR

I *(name)* _____declare that:

- I explained the information in this document to (*name of child and parent)*_____
  I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understand all aspects of the research, as discussed above.
- I did/did not use an interpreter (*if an interpreter is used, then the interpreter must sign the declaration below).*

Signed at (*place*) _____on (*date*) _____20_____

_____
Signature of investigator

DECLARATION BY INTERPRETER

I *(name)* _____.declare that:

- I assisted the investigator (*name*) _____
  to explain the information in this document to
  (*name of parent/legal guardian*) _____
  using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the parent/legal guardian fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.

Signed at (*place*) _____on (*date*) _____20_____

_____
Signature of interpreter

APPENDIX C

DEMOGRAPHICS QUESTIONNAIRE

A. PARENT / CAREGIVER DEMOGRAPHICS

Sex: MALE FEMALE
Age: _____
DOB: _____
Marital status: MARRIED SINGLE DIVORCED WIDOWED
Race: WHITE COLOURED BLACK AFRICAN OTHER
Religion: _____
Home Language / Mother Tongue: ENGLISH AFRIKAANS isiXHOSA OTHER
Other languages in which you are fluent: _____
Employed: YES NO
If YES, please describe what type of work you do:
_____
Are you dependent on a disability grant? YES NO

B. OBSTETRICS HISTORY

Any birth complications: YES NO
If yes, please specify:
_____
Emergency C-section: YES NO
If yes, please explain:
_____
Routine checkups followed: YES NO
If no, why not:
_____
Alcohol use during pregnancy: YES NO
If yes, please explain (frequency and quantity):
_____
Drug use during pregnancy: YES NO
If yes, please explain (quantity, frequency and type):
_____

C. CHILD / PATIENT DEMOGRAPHICS

Sex: MALE FEMALE
Age: _____
DOB: _____
Race: WHITE COLOURED BLACK AFRICAN OTHER
Religion: _____

Home Language / Mother Tongue: ENGLISH AFRIKAANS isiXhosa
OTHER
Other languages in which your child is fluent: _____

D. CHILD / PATIENT MEDICAL HISTORY

Most recent CD4 count: _____ Date taken: _____
Most recent viral load: _____ Date taken: _____

Significant / traumatic head injuries: YES NO
If yes, please specify the following:
When/how long ago:
_____
Was child unconscious (could not wake child up):
_____
Was child hospitalised and for how long:
_____
Did the child require stitches:
_____
Brain scans done and when:
_____

Alcohol use: Previous YES NO
Alcohol use: Current YES NO
If yes, please specify quantity and frequency:
_____

Drug use: Previous YES NO
Drug use: Current YES NO
If yes, please specify quantity, frequency and type:
_____
_____

Has your child ever been diagnosed with any psychiatric illness: eg: depression, psychosis, anxiety, etc: YES NO
If yes, please specify:
_____
Is your child currently receiving treatment for a psychiatric illness: YES NO
If yes, please explain:
_____

Please explain your child's current HAART treatment regime:
_____
_____
_____

Has your child had any HIV related illnesses: YES NO

If yes, please specify: eg: TB, pneumonia, meningitis, etc.
_____
_____

Is your child currently receiving treatment for an HIV related illness: YES NO
If yes, please explain:
_____

Has your child had any surgical procedures done? Please explain:
_____
_____
_____

Does your child have any other medical conditions: YES NO
If yes, please specify: eg: diabetes, asthma, epilepsy, etc:
_____
_____

E. EDUCATION LEVEL OF CHILD

Highest grade completed at school:
_____
Current grade:
_____
If child is not presently attending school, please specify their daily activities. Are they at home? At a care facility?
_____
Has he/she repeated any grades at school? YES NO
School setting: RURAL URBAN

F. GENERAL INFORMATION

Which best describes the area you live in?
SURBURBAN URBAN RURAL
TOWNSHIP
What is the name of the area you live in?
_____
Size of the house (number of rooms in the house):
_____
Number of people who live in the house:
_____
Who lives in your house (e.g., father, mother, grandmother, etc):
_____

Annual Household Income:

i.	0 – 35 000	☐
ii.	36 000 – 50 000	☐
iii.	51 000 – 80 000	☐
iv.	81 000 – 100 000	☐
v.	101 000 – 120 000	☐
vi.	121 000 – 150 000	☐
vii.	151 000 and more	☐

Do you have the following amenities at home:

i.	Tap with running water		YES		NO
ii.	Electricity / Gas		YES		NO
iii.	Flush toilet in house	YES		NO	
iv.	TV	YES		NO	
v.	Adequate clothing for child	YES		NO	
vi.	Enough food to eat for at least 2meals per day		YES		NO
vii.	Child's own study/homework area or space	YES		NO	

APPENDIX D

Table 14

Scale scores for the CBCL

Scale	Normal Range	Borderline Clinical Range	Clinical Range
Total Competence	40-80	35-40	10-35
Activities	35-65	30-35	20-30
Social	35-65	30-35	20-30
School	35-65	30-35	20-30
Total Problems	50-60	60-65	65-100
Internalizing Problems	50-60	60-65	65-100
Anxious/Depressed	50-65	65-70	70-100
Withdrawn/Depressed	50-65	65-70	70-100
Somatic Complaints	50-65	65-70	70-100
Externalizing Problems	50-60	60-65	65-100
Rule-Breaking Behaviour	50-65	65-70	70-100
Aggressive Behaviour	50-65	65-70	70-100

Notes. Activities refer to participation in sports, skills in activities, jobs and chores. Social refers to participation in organisations, number of friends, contact with friends and behaviours with others and alone. School refers to mean performance at school, special classes, repeated grades and school problems. Anxious/Depressed refers to crying, fearful, unloved, worthless, nervous, guilty, self-conscious, talk of suicide, worries. Withdrawn/Depressed refers to enjoying little, preferring to be alone, won't talk, secretive, shy, lacks energy, sad and withdrawn. Somatic Complaints refers to nightmares, constipated, dizzy, tired, aching, headaches, nausea, eye and skin problems, stomach problems and vomiting.
Rule-Breaking Behaviour refers to drinking alcohol, not feeling guilty, breaking rules, bad friends, cheating, runs away, sets fires, sex problems, steals, swears, thinks about sex, uses drugs and vandalism.
Aggressive Behaviour refers to argumentative, mean, destroys own and others things, disobeys at home and school, fights, attacks, screams, stubborn, mood changes, sulks, suspicious, teases, temper, threaten, and loud.

APPENDIC E

Table 8.

Qualitative Descriptions of WASI Scores

IQ Scores	Subtest Scaled Score	Classification
130 and above	16 – 19	Very Superior
120 – 129	14 – 15	Superior
110 – 119	12 – 13	High Average
90 – 109	8 – 11	Average
80 – 89	6 – 7	Low Average
70 – 79	4 -5	Borderline
69 and below	1 – 3	Extremely Low

Note. Taken from *Wechsler Abbreviated Scale of Intelligence*(Wechsler, 1999)

APPENDIX F

Table 5.

Qualitative Descriptions of NEPSY-II Scaled Scores

Scaled Score	Classification
13 – 19	Above Expected Level
8 – 12	At Expected Level
6 – 7	Borderline
4 – 5	Below Expected Level
1 – 3	Well Below Expected Level

Note. Taken from *NEPSY-II* (Korkman, Kirk & Kemp, 2007).

APPENDIX G

Table 15
Case 1:SG: Reliable change index scores

Measure	RCI score
PIQ	-0.95
DKEFS	
Letter Fluency	0.07
Category Fluency	0.39
BNT-SF	0.15
WISC	
Digit Span (total)	0
Processing Speed	-1.56
Colour Trail 1	0.57
Colour Trail 2	1.73*
Grooved Pegboard DH	1.35
Grooved Pegboard NDH	1.55
Fingertip Tapping DH	-0.15
Fingertip Tapping NDH	0.9
RCF	
Copy	1.2
Recall	1.41
Delay	0.4
HVLT	0.38

Notes. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remembered after three trials.An RCI score greater than 1.64 indicates a significant change, while a RCI score less than 1.64 indicates a change that is not significant. *Indicates significant change

Table 16

Case 2:KF: Reliable change index scores

Measure	RCI score
PIQ	1.08
DKEFS	
Letter Fluency	0.37
Category Fluency	0.39
NEPSY-II	
Naming	-0.56
Inhibition	0.26
Switching	-0.15
BNT-SF	0.92
WISC	
Digit Span (total)	-1.34
Processing Speed	0.24
Colour Trail 1	0.06
Colour Trail 2	-0.78
Grooved Pegboard DH	-0.03
Grooved Pegboard NDH	0.05
Fingertip Tapping DH	-0.15
Fingertip Tapping NDH	0
RCF	
Copy	-0.83
Recall	-1.25
Delay	-0.98
HVLT	-1.05

Notes. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remembered after three trials.An RCI score greater than 1.64 indicates a significant change, while a RCI score less than 1.64 indicates a change that is not significant. *Indicates significant change

Table 17

Case 3:EN: Reliable change index scores

Measure	RCI score
PIQ	-0.61
BNT-SF	-0.62
WISC	
Digit Span (total)	1.34
Processing Speed	0.84
Colour Trail 1	-1.62
Colour Trail 2	-0.39
Grooved Pegboard DH	-1
Grooved Pegboard NDH	-0.58
Fingertip Tapping DH	1.07
Fingertip Tapping NDH	-0.3
RCF	
Copy	0.94
Recall	0.5
Delay	1.48
HVLT	1.1

Notes. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remembered after three trials.An RCI score greater than 1.64 indicates a significant change, while a RCI score less than 1.64 indicates a change that is not significant. *Indicates significant change

Table 18

Case 4:TD: Reliable change index scores

Measure	RCI score
PIQ	08-Jan
DKEFS	
Letter Fluency	0.96
Category Fluency	0.7
NEPSY-II	
Naming	-1.05
Inhibition	-0.78
Switching	-1.32
BNT-SF	0.92
WISC	
Digit Span (total)	
Processing Speed	-0.36
Colour Trail 1	1.07
Colour Trail 2	-0.49
Fingertip Tapping DH	-0.88
Fingertip Tapping NDH	-1.51
RCF	
Copy	-0.4
Recall	0
Delay	-0.06
HVLT	-1.05

Notes. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remembered after three trials.An RCI score greater than 1.64 indicates a significant change, while a RCI score less than 1.64 indicates a change that is not significant. *Indicates significant change

Table 19

Case 5:AX: Neuropsychological test performance

Measure	RCI score
PIQ	-0.61
DKEFS	
Letter Fluency	-1.39
Category Fluency	-1.48
NEPSY-II	
Naming	0.43
Inhibition	1.3
Switching	1.02
BNT-SF	-1.38
WISC	
Digit Span (total)	-0.45
Processing Speed	0.84
Colour Trail 1	0.02
Colour Trail 2	-0.08
Grooved Pegboard DH	-0.43
Grooved Pegboard NDH	-0.55
Fingertip Tapping DH	0.52
Fingertip Tapping NDH	0.9
RCF	
Copy	-0.91
Recall	-0.67
Delay	-0.83
HVLT	0.62

Notes. DH refers to dominant hand. NDH refers to non-dominant hand. HVLT total score refers to the total number of words remembered after three trials.An RCI score greater than 1.64 indicates a significant change, while a RCI score less than 1.64 indicates a change that is not significant. *Indicates significant change